Mathematical and Theoretical Biology. Mathematical and Molecular Biophysics

Volume 2: Mathematical Biophysics and Molecular Biology

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Molecular biologists and biophysicists

John Randall (physicist)

Sir John Turton Randall,DSc, FRSE	
Sir John Turton Randall, FRSE at King's	
Born	March 23, 1905 Newton-le-Willows, St Helens, Lancashire, UK
Died	June 16, 1984 Edinburgh
Residence	UK
Citizenship	United Kingdom of Great Britain
Nationality	British
Ethnicity	British, Scottish descent
Fields	Experimental physicist and biophysicist
Institutions	GEC, The Cavendish Laboratory of the University of Cambridge, King's College in the University of London and *Dept. of Zoology* at the University of Edinburgh
Alma mater	University of Manchester and The Cavendish Laboratory of the University of Cambridge
Doctoral advisor	Nobel-prize winner, Sir-William Lawrence Bragg, Head of The Cavendish Laboratory
Doctoral students	49
Known for	High-power, multi-cavity magnetron for British and American radar stations in WWII, DNA structure determination, neutron diffraction studies of labelled proteins
Influenced	discovery of A- and B- DNA double helix structures, Maurice F. Wilkins, Rosalind Franklin
Notable awards	Knight of the British Empire, FRSE

Sir John Turton Randall,FRSE, (March 23, 1905 − June 16, 1984) was a British physicist and biophysicist, credited with radical improvement of the cavity magnetron, an essential component of centimetric wavelength radar, which was one of the keys to the Allied victory in the Second World War. It is also the key component of microwave ovens. He also led the King's College London team which worked on the structure of DNA; his deputy, Professor Maurice Wilkins, shared the 1962 Nobel Prize for Physiology or Medicine, together with James Watson and Francis Crick of the Cavendish Laboratory at the University of Cambridge, for the determination of the structure of DNA. His other staff included Rosalind Franklin, Raymond Gosling, Alex Stokes and Herbert Wilson, all involved in research on DNA.

Origins

John Randall was born on 23 March 1905 at Newton-le-Willows, St Helens, Lancashire, the only son and the first of the three children of Sidney Randall, nurseryman and seedsman, and his wife, Hannah Cawley, daughter of John Turton, colliery manager in the area. He was educated at the grammar school at Ashton-in-Makerfield and at the University of Manchester, where he was awarded a first-class honors degree in physics and a graduate prize in 1925, and an MSc in 1926. He married Doris, daughter of Josiah John Duckworth, a colliery surveyor, in 1928. They had one son.

From 1926 to 1937 Randall was employed on research by the General Electric Company at its Wembley laboratories, where he took a leading part in developing luminescent powders for use in discharge lamps. He also took an active interest in the mechanisms of such luminescence.

The Magnetron

By 1937 he was recognized as the leading British worker in his field, and was awarded a Royal Society fellowship to the University of Birmingham, where he worked on the electron trap theory of phosphorescence in Professor Marcus Oliphant's physics faculty. When the war began in 1939 Randall transferred to the large group working on centimeter radar. At the time limited transmitter output was the greatest single obstacle in the development of this type of radar.

Simple two-pole magnetrons had been developed in the 1920s but gave relatively low power outputs. A more powerful multi-cavity resonant magnetron had been developed in 1935[1] by Hans Erich Hollmann in Berlin. By 1940 Randall and Dr Harry Boot produced a working prototype similar to Hollman's cavity magnetron, but added liquid cooling and a stronger cavity. However Randall and Boot soon managed to increase its power output 100-fold. As Prof. W. E.Burcham recollects: "*John Randall and Harry Boot, two young physicists were assigned to the task. Within 2 months (21st February 1940) they had produced a new kind of magnetron, one with 8 concentric cavities… Randall got the inspirational idea of using 8 cavities when he researched the design of the original Hertz oscillator which was an open single ring. Randall saw that this structure could be extrapolated into a cylinder and then into 8 resonating chambers* "[2] . Later James Sayers provided the final breakthrough to a practical magnetron device for use in radar stations. At the same time, the Telefunken Company of Berlin was also 'searching' for such a device[3] , but has apparently met with much less success than the British inventors or the Romanian Professor Theodor V. Ionescu who was also engaged at the time in the same quest for a powerful magnetron. However, the split anode magnetron had first been developed in 1921 by Dr. A.E.Hull at GEC Company in USA; also in 1921, Haben, who was working in Germany, developed a similar device that worked on a 3 cm wavelength. A strong competitor of the former inventors was also Dr. H.E.Hollman who registered many patents between 1925 and 1935 that documented devices related to magnetron development[4] .

The military importance of a high-power multi-cavity magnetron was immense to the British defense at first, and then to the American AirForce offense in the North Sea and the Pacific. Centimetric radar could detect much smaller objects. The combination of the small-sized cavity magnetron, small antennas and high resolution allowed small high quality radars to be installed in aircraft to detect submarines and other aircraft. This advance eventually defeated the German U-boats and so won the Battle of the Atlantic. This allowed Britain to be supplied and then re-armed from across the Atlantic, ultimately allowing for the the liberation of continental Europe. Other applications of radar included aerial interception of bombers at night, better navigation of Allied bombers (H2S radar), better anti-aircraft batteries and naval gunnery and proximity fuzes. One million magnetrons were produced by Bell Labs alone in the USA before the end of the war, and many millions since have been incorporated into cookers and a wide range of other appliances. An official American historian described Magnetron Number 12 that was taken to the USA in September 1940 as follows: "When the members of the Tizard Mission brought one to America in 1940, they carried the most valuable cargo ever brought to our shores."

As an important spin off from the magnetron war efforts at MIT was, shortly after WWII, American physicist Erwin L. Hahn's discovery at MIT of the nuclear magnetic resonance phenomenon, a key tool for modern chemistry and physics research[5] [6] .

In 1943 Randall left Oliphant's physical laboratory at Birmingham to teach for a year in the Cavendish Laboratory at Cambridge. In 1944 Randall was appointed professor of natural philosophy at University of St Andrews and began planning research in biophysics (with Maurice Wilkins) on a small Admiralty grant.

Double Helix Discovery

William Astbury

Oswald Avery

Francis Crick

Erwin Chargaff

Max Delbrück

Jerry Donohue

Rosalind Franklin

Raymond Gosling

Phoebus Levene

Linus Pauling

Sir John Randall

Erwin Schrödinger

Alex Stokes

James Watson

Maurice Wilkins

Herbert Wilson

King's College London

In 1946, John T Randall- who had as Ph.D. advisor the Nobel-Prize winning physicist, William Lawrence Bragg- was appointed Head of Physics Department at King's College in London. He then moved to the Wheatstone chair of physics at King's College London, where the Medical Research Council set up the Biophysics Research Unit with Randall as the director (now known as Randall Division of Cell and Molecular Biophysics) at King's College London. During his term as Director the experimental work leading to the discovery of the structure of DNA was made there by Rosalind Franklin, Raymond Gosling, Maurice Wilkins, Alex Stokes and Herbert R. Wilson. He assigned Raymond Gosling as a PhD student to Dr. R. Franklin to work on DNA structure by X-ray diffraction.

Maurice Wilkins shared the 1962 Nobel Prize for Physiology and Medicine with James Watson and Francis Crick; Rosalind Franklin had already died from cancer in 1958.

In addition to the X-Ray diffraction work the unit conducted a wide-ranging programme of research by physicists, biochemists, and biologists. The use of new types of light microscopes led to the important proposal in 1954 of the sliding filament mechanism for muscle contraction. Randall was also successful in integrating the teaching of biosciences at King's College.

In 1951 he set up a large multidisciplinary group working under his personal direction to study the structure and growth of the connective tissue protein collagen. Their contribution helped to elucidate the three-chain structure of the collagen molecule. Randall himself specialized in using the electron microscope, first studying the fine structure of spermatozoa and then concentrating on collagen. In 1958 he began to study the structure of protozoa. He set up a new group to use the cilia of protozoa as a model system for the analysis of morphogenesis by correlating the structural and biochemical differences in mutants.

Later years

In 1970 he retired to Edinburgh University, where he formed a group which applied a range of new biophysical methods, such as coherent neutron diffraction studies of protein crystals in ionic solutions in heavy water, to study by neutron diffraction and scattering various biomolecular problems, such as the proton exchange of protein residues by deuterons. He continued such work with characteristic vigor supported by a few loyal assistant crystallographers until his death.

In science Randall was not just original but a maverick. He made extremely important contributions to biological science when he set up, at the right time, a large multidisciplinary biophysical laboratory where his staff were able to achieve much success. However his treatment of Rosalind Franklin upon her leaving King's for Birkbeck College is still a matter of debate and controversy, as already touched upon above.

His direct, personal contributions to experimental biophysics at a later stage were possibly not as outstanding as those he made in experimental physics early in his life. In science, and elsewhere, he showed most of the times excellent judgement. He had a rare, unusual capacity to see the essentials of a situation and also had outstanding skill in obtaining funds and buildings for research, possibly owed in part to his support by his former X-ray adviser Sir William Lawrence Bragg. He was thought by some to be ambitious and to enjoy 'political' power, but his ambitions were actually motivated only by the common good, as in the case of the magnetron invention that has been said many times to have saved Great Britain from nazi invasion and possible occupation. On the other hand, he was a very warm and considerate person, of unusual modesty, and also with a deep understanding of physics, especially in the experimental areas of X-ray and neutron diffraction. The informal and democratic side of his character may have appeared to some to contrast with his natural self-assertion. He showed great dedication and enthusiasm in his scientific work, just as he did in the extensive gardening he much enjoyed in his spare time in Edinburgh.

Honors

In 1938 Randall was awarded a DSc by the University of Manchester. In 1943 he was awarded (with H. A. H. Boot) the Thomas Gray memorial prize of the Royal Society of Arts for the invention of the cavity magnetron. In 1945 he became Duddell medallist of the Physical Society of London and shared a payment from the Royal Commission on Awards to Inventors for the magnetron invention, and in 1946 he was made a fellow of the Royal Society and became its Hughes medalist. Further awards (with Boot) for the magnetron work were, in 1958, the John Price Wetherill medal of the Franklin Institute of the state of Pennsylvania and, in 1959, the John Scott award of the city of Philadelphia. In 1962 he was knighted, and in 1972 he became a fellow of the Royal Society of Edinburgh.

It can be said that John Randall's contribution to the discovery of the structure of DNA has effectively gone 'unrecognized' although the award of a third of the 1962 Nobel Prize for Physiology or Medicine to Maurice Wilkins reflected the contribution made by all the members of staff in the King's College Laboratory; the new DNA sculpture at Clare College, Cambridge has the following words: On the base: "These strands unravel during cell reproduction.

Genes are encoded in the sequence of bases."and "The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins.", as well as on the helices: "The structure of DNA was discovered in 1953 by Francis Crick and James Watson while Watson lived here at Clare." and "The molecule of DNA has two helical strands that are linked by base pairs Adenine - Thymine or Guanine - Cytosine."

So no mention is made of either Sir Lawrence Bragg [already a Nobel Prize winner] director of the Cambridge's Cavendish Laboratory or Sir John Randall, the director of King's College's laboratory, London [not a Nobel Prize winner]; in 1962 four members of the Cavendish Laboratory received shares of Nobel Prizes: Francis Crick, John Kendrew, Max Perutz, and James Watson - while only one member of King's College, London received a share of the Nobel Prize (Maurice Wilkins) and that was shared with Crick and Watson. Unfortunately Rosalind Franklin had already died of cancer in 1958, possibly related to her exposure to X-rays in her experimental work; subsequent debate has been whether Franklin 'deserved' a share of the Nobel Prize posthumously. Nobel Prizes are not awarded posthumously.

According to Wilkins, Randall wanted to be more directly involved in the work leading to the discovery of the structure of DNA but yet had previously turned down Francis Crick from working alongside Wilkins at King's College, London; the loss of Crick to King's was a gain to the Cavendish Laboratory, but the unofficial liaison between Crick and Wilkins helped the Cavendish Laboratory 'win' both of the DNA races: with Linus Pauling and with King's College, London.

Sir John Randall missed his opportunity to also add his own name to the double helix structure of A-DNA --in the same way as Crick, Watson, and Wilkins did; he could have done it by agreeing to a joint publication by the two research teams as proposed by Sir Lawrence Bragg, even though he was a leading player in the race. One cannot imagine that either Franklin or Wilkins would have been happy merely with the phrase: *"The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins"*, but Sir John Randall felt he had good cause to be unhappy with his laboratory's competitors from the Cavendish Laboratory, Cambridge, and also with Sir William Lawrence Bragg--the Head of the Cavendish Laboratory at the time, for his handling of the informal collaborations between the two research teams involved. He was also reported to have been unhappy with Dr. Rosalind Franklin for her stubbornly strong opposition to the double helix model of A-DNA which was reflected in his parting letter to Dr. Rosalind Franklin who left King's for Birkbeck College in London. One notes however that Sir William had been Dr. Randall' s scientific adviser in his early X-ray studies, and that without the latter's support for obtaining substantial research funding he might not have been able to establish his new Biophysics and X-ray diffraction laboratories at King's.

At the same time it can be said that Wilkins wished that his own name too had been joined with those of Watson and Crick in 1953 when invited to be listed as an author of the first Watson/Crick paper. Both Randall and Wilkins deserve more recognition of the discovery of the structure of DNA, but unlike John Randall, Wilkins at least got his one third share of the 1962 Nobel Prize for Physiology or Medicine.

Books featuring Sir John Randall, FRSE

- Chomet, S. (Ed.), *D.N.A. Genesis of a Discovery*, 1994, Newman- Hemisphere Press, London.
- Wilkins, Maurice, *The Third Man of the Double Helix: The Autobiography of Maurice Wilkins.* ISBN 0-19-860665-6.
- Ridley, Matt; "Francis Crick: Discoverer of the Genetic Code (Eminent Lives)" first published in July 2006 in the USA and then in the UK. September 2006, by HarperCollins Publishers ISBN 0-06-082333-X.
- Tait, Sylvia & James "A Quartet of Unlikely Discoveries" (Athena Press 2004) ISBN 184401343X
- Watson, James D., The Double Helix: A Personal Account of the Discovery of the Structure of DNA, Atheneum, 1980, ISBN 0-689-70602-2 (first published in 1968).

See also

- Magnetron
- A magnetron precursor prototype in 1935

External links

- Biography and picture of John Randall at the King's College website [7]
- Randall Division of Cell and Molecular Biophysics website [8]
- Key Participants: J. T. Randall [9] - *Linus Pauling and the Race for DNA: A Documentary History*

References

[1] RadarWorld (http://www.radarworld.org/hans4.html)

[2] "Radar Recollections - A Bournemouth University/CHiDE/HLF project" by Prof. W. E. Burcham (http://histru.bournemouth.ac.uk/ Oral_History/Talking_About_Technology/radar_research/the_magnetron.html)

[3] From the 1935 magazine *Electronics*: "Microwaves To Detect Aircraft" (http://histru.bournemouth.ac.uk/Oral_History/ Talking_About_Technology/radar_research/the_magnetron.html)

[4] "Radar Recollections - A Bournemouth University/CHiDE/HLF project" (http://histru.bournemouth.ac.uk/Oral_History/ Talking_About_Technology/radar_research/the_magnetron.html)

[5] Hahn,E.1950. *Phys.Rev.* **80**:1070-1084

[6] *Pulsed magnetic resonance--NMR, ESR, and optics: a recognition of E.L. Hahn*. Oxford University Press. 1992. ISBN 0198539622.

[7] http://www.kcl.ac.uk/about/history/archives/dna/individuals/randall.html

[8] http://www.kcl.ac.uk/schools/biohealth/research/randall/

[9] http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/people/randall.html

Herbert Wilson

Herbert R. Wilson, F.R.S	
Born	20 March 1929 Wales
Died	22 May 2008 (aged 79) Stirling
Nationality	United Kingdom
Fields	Physics and Biophysics
Institutions	King's College at the University of London, Queen's College at the University of Dundee, University of St. Andrews, University of Stirling
Alma mater	King's College at the University of London, University of Wales at Bangor
Notable awards	Fellow of The Royal Society

Professor Herbert R. Wilson, F.R.S. (1929 —2008) was a physicist, who was one of the team who worked on the structure of DNA at King's College London, under the direction of Sir John Randall.

Biography

College education

On a fellowship of the University of Wales, Herbert R. Wilson joined Maurice Wilkins at King's College London in September 1952. The work involved X-ray diffraction studies of DNA, nucleoproteins and cell nuclei. Prior to the double helix model, their studies showed that DNAs from different sources (including biologically active transforming principle) had essentially the same structure, and confirmed that the phosphate groups were on the outside of the molecule.

Scientific discoveries and achievements

- *Emeritus Professor Herbert R. Wilson, FRS, with the Double Helix molecular model of A-DNA in front of King's College in London.*

Three papers were published in Nature in April 1953 to announce a structure for DNA. Maurice Wilkins, Alex Stokes and Wilson published their paper in the same issue as the paper from Rosalind Franklin and Raymond Gosling, and the paper by Francis Crick and James Watson. The 1962 Nobel Prize for Physiology or Medicine was subsequently jointly awarded to Francis Crick, James Watson, and Maurice H.F. Wilkins.

Unfortunately in his autobiography "*The Third Man of The Double Helix*", Maurice H.F. Wilkins does not specifically credit Stokes, Wilson and several other co-authors of his papers in "*Nature*"[1] , [2] ; whether this was deliberate on his part or just down to rather poor sub-editing by OUP is debatable; however, it is most likely to have been a matter of mere 'expedience', as there were more than five co-authors on several of his later papers on the

subject published in either *Nature* or, subsequently, in the *Journal of Molecular Biology*[3] ,[4] ,[5] ,[6] . Nevertheless, both he and Alex Stokes are currently recognized at King's College as two of the eight key researchers that contributed to the discovery of the structure of the A-DNA crystalline structure.

Following the publication of the double helical structure in 1953, Wilson participated in the refinement of the DNA structure in Wilkins' group. In 1957 Professor Wilson was appointed Lecturer in Physics at Queen's College, Dundee, then at University of St Andrews, became a Senior Lecturer in 1964, and then Reader at the University of Dundee in 1973. In 1962 he was Visiting Research Associate at the Children's Cancer Research Foundation, Boston Mass. In 1983 he was appointed Professor of Physics at the University of Stirling (now Emeritus). His research at Dundee and Stirling has involved X-ray crystallographic studies of nucleic acid components and their analogues, and structural studies of flexuous viruses. He was awarded an Honorary Fellowship by the University of Wales, Bangor in 2005.

As a Welshman Herbert was honored by The National Eisteddfod in Wales by being given the official white robe.

After suffering from terminal cancer, Wilson died on May 22, 2008. He was survived by his wife, two daughters, and two grandchildren; his son predeceased him in 1996.

Books and articles by Herbert R. Wilson, FRS

Books

- Herbert R. Wilson. 1966. *Diffraction of X-rays by Proteins, Nucleic Acids and Viruses.*[7] [8] , London: Arnold publs.

Original articles

- Wilkins, M.H.F., Stokes, A.R. and H.R. Wilson.(1953). *Nature*, **171**, 737.
- Wilkins, M.H.F., Seeds, W.E., Stokes, A.R. and H.R. Wilson.(1953). *Nature*, **171**, 759.
- Wilkins, M.H.F., Zubay, G. and H.R. Wilson. (1959). *J. Mol. Biol*., **1**, 179.
- H.R. Wilson. (with Feughelman, M., & Langridge, R. et al).(1955). *Nature*, **175**, 834.
- H.R. Wilson. (with Langridge, R. et al). (1960). *J. Mol. Biol.*, **2**, 19.
- H.R. Wilson. (with Langridge, R, et al). (1960). *J. Mol. Biol.*, **2**, 38.
- H.R. Wilson. (with Fuller, W. et al). (1965). *J. Mol. Biol.*, **12**, 60.

Books featuring Herbert R. Wilson, FRS

- Chomet, S. (Ed.), *D.N.A. Genesis of a Discovery*, 1994, Newman- Hemisphere Press, London; NB a few copies are available from Newman-Hemisphere at 101 Swan Court, London SW3 5RY (phone: 07092 060530).
- Wilkins, Maurice, The Third Man of the Double Helix: The Autobiography of Maurice Wilkins ISBN 0-19-860665-6.
- Ridley, Matt; "Francis Crick: Discoverer of the Genetic Code (Eminent Lives)" was first published in June 2006 in the USA and then in the UK September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X. [This short book is in the publisher's "Eminent Lives" series.]
- Contributed book: *Mathematical and Experimental Biophysicists: Biographies and Related Fields*, (Bci2, ed.), pp.382, 31 January 2010, v.7. in Wikipedia [9]
- Tait, Sylvia & James "A Quartet of Unlikely Discoveries" (Athena Press 2004) ISBN 184401343X

External links

- King's College London link [10]
- Photos at 40th anniversary [11] (From left: Raymond Gosling, Herbert Wilson, Maurice Wilkins and Alec Stokes)
- 'Death' of D.N.A. Helix (Crystaline) joke funeral card [12].
- First press stories on D.N.A. [13]

References

[1]   Wilkins, M.H.F., Stokes, A.R. and H.R. Wilson.(1953). *Nature*, **171**, 737

[2]   Wilkins, M.H.F., Seeds, W.E., Stokes, A.R. and H.R. Wilson.(1953). *Nature*, **171**, 759

[3]   H.R. Wilson. (with Feughelman, M., & Langridge, R. et al).(1955). *Nature*, **175**, 834

[4]   H.R. Wilson. (with Langridge, R. et al). (1960). *J. Mol. Biol.*, **2**, 19

[5]   H.R. Wilson. (with Langridge, R, et al). (1960). *J. Mol. Biol.*, **2**, 38

[6]   H.R. Wilson. (with Fuller, W. et al). (1965). *J. Mol. Biol.*, **12**, 60

[7]   Cited in *Physical Chemistry of Food Processes*, Vol.**1**, p.204 (1992),New York, N.Y.: Van Nostrand-Reinhold

[8]   Cited in a recently contributed book: *Mathematical and Experimental Biophysicists: Biographies and Related Fields*, (Bci2, ed.), pp.382, 31 January 2010, v.7. in Wikipedia (http://en.wikipedia.org/wiki/User:Bci2/Books/MathematicalBiophysicists)

[9]   http://en.wikipedia.org/wiki/User:Bci2/Books/MathematicalBiophysicists

[10]   http://www.kcl.ac.uk/about/history/archives/dna/individuals/wilson

[11]   http://www.kcl-cdu.org.uk/dna_strand_kcl.jpg

[12]   http://en.wikipedia.org/wiki/Image:Rosalindfranklinsjokecard.jpg

[13]   http://www.packer34.freeserve.co.uk/selectedTATAwebsites.htm

Erwin Chargaff

Erwin Chargaff (Czernowitz, August 11, 1905 – New York City, USA, June 20, 2002) was an Austrian Jewish biochemist who emigrated to the United States during the Nazi era. Through careful experimentation, Chargaff discovered two rules that helped lead to the discovery of the double helix structure of DNA.

Chargaff had one son, Thomas, with his wife Vera Broido, whom he married in 1928. Chargaff became an American citizen in 1940.

Early life

Chargaff was born in Czernowitz on August 11, 1905, Bukowina, Austria, which is now Chernovtsy, Ukraine.[1] Chargaff had a difficult time deciding whether he would pursue science or philology as a career: he had a natural gift for languages, and over the course of his life he would learn 15. His American colleagues recalled that he could speak English better than they could.[1]

From 1924 to 1928, Chargaff studied chemistry in Vienna, receiving a doctorate. From 1928 to 1930, Chargaff served as the Milton Campbell Research Fellow in organic chemistry at Yale University, but he did not like New Haven, Connecticut. Chargaff returned to Europe, where he lived from 1930 to 1934, serving first as the assistant in charge of chemistry for the department of bacteriology and public health at the University of Berlin (1930-1933), and then as a research associate at the Pasteur Institute in Paris (1933-1934).[1]

He had published 30 papers by the time he reached 30 years of age.[1]

Columbia University

Chargaff emigrated to New York in 1935, taking a position as a research associate in the department of biochemistry at Columbia University, where he spent most of his professional career. Chargaff became an assistant professor in 1938 and a professor in 1952. After serving as department chair from 1970 to 1974, Chargaff retired to professor emeritus. After his retirement to professor emeritus, Chargaff moved his lab to Roosevelt Hospital, where he continued to work until 1992. He retired in 1992.

During his time at Columbia, Chargaff published numerous scientific papers, dealing primarily with the study of nucleic acids such as DNA using chromatographic techniques. He became interested in DNA in 1944 after Oswald Avery identified the molecule as the basis of heredity. In 1950, he discovered that the amounts of adenine and thymine in DNA were roughly the same, as were the amounts of cytosine and guanine. This later became known as the first of Chargaff's rules.

Honors awarded to him include the Pasteur Medal (1949) and the National Medal of Science (1974).

Chargaff's rules

Erwin Chargaff proposed two main rules in his lifetime which were appropriately named Chargaff's rules. The first and best known achievement was to show that in natural DNA the number of guanine units equals the number of cytosine units and the number of adenine units equals the number of thymine units. In human DNA, for example, the four bases are present in these percentages: A=30.9% and T=29.4%; G=19.9% and C=19.8%. This strongly hinted towards the base pair makeup of the DNA, although Chargaff was not able to make this connection himself. For this research, Chargaff is credited with disproving the tetranucleotide hypothesis (Phoebus Levene's widely accepted hypothesis that DNA was composed of a large number of repeats of GACT). Most workers had previously assumed that deviations from equimolar base ratios (G = A = C = T) were due to experimental error, but Chargaff documented that the variation was real, with [C + G] typically being slightly less abundant. He was able to do this with the newly developed paper chromatography and ultraviolet spectrophotometer. Chargaff met Francis Crick and James D. Watson at Cambridge in 1952, and, despite not getting on well with them personally, explained his findings to them. Chargaff's research would later help Watson and Crick to deduce the double helical structure of DNA.

The second of Chargaff's rules is that the composition of DNA varies from one species to another, in particular in the relative amounts of A, G, T, and C bases. Such evidence of molecular diversity, which had been presumed absent from DNA, made DNA a more credible candidate for the genetic material than protein.

Besides making these important steps toward the structure of DNA, Chargaff's lab also conducted research on the metabolism of amino acids and inositol, blood coagulation, lipids and lipoproteins, and the biosynthesis of phosphotransferases.

Later life

Beginning in the 1950s, Chargaff became increasingly outspoken about the failure of the field of molecular biology, claiming that molecular biology was "running riot and doing things that can never be justified." He believed that human knowledge will always be limited in relation to the complexity of the natural world, and that it is simply dangerous when humans believe that the world is a machine, even assuming that humans can have full knowledge of its workings. He also believed that in a world that functions as a complex system of interdependency and interconnectedness, genetic engineering of life will inevitably have unforeseen consequences. Chargaff warned that "the technology of genetic engineering poses a greater threat to the world than the advent of nuclear technology. An irreversible attack on the biosphere is something so unheard of, so unthinkable to previous generations, that I only wish that mine had not been guilty of it."

After Francis Crick, James Watson and Maurice Wilkins received the 1962 Nobel Prize for their work on discovering the double helix of DNA, Chargaff withdrew from his lab and wrote to scientists all over the world

about his exclusion.[2] [1] Chargaff was a notable exclusion, along with the deceased Rosalind Franklin, from the 1962 Nobel Prize for DNA discovery. Along with Chargaff, 23 other scientists contributed significantly to the double helix elucidation and were not rewarded with the Nobel for their work towards the double helix.[1] Thus, only the people at 'the top of the pyramid' were rewarded for their genius, but all of those who provided supporting material are well recognised by their peers, if not the public or the media.

Books authored

Chargaff wrote 450 papers and 15 books on diverse topics during his retirement years.[1]

- Erwin Chargaff, *Heraclitean Fire: Sketches from a Life Before Nature* (1978). Rockefeller University Press: ISBN 0-87470-029-9; 252 p.

- Serious Questions, An ABC of Sceptical Reflections. Boston, Basel, Stuttgart: Birkhäuser, 1986

See also

- Nobel Prize controversies

References

[1] Christy, Nicholas (Winter 2004). "Faculty Remembered" (http://www.cumc.columbia.edu/news/journal/journal-o/winter-2004/faculty. html). 'Columbia University P&S Journal. . *Retrieved 2007-08-04.*

[2] Judson, Horace (2003-10-20). "No Nobel Prize for Whining" (http://query.nytimes.com/gst/fullpage.html?sec=health& res=9C02E4DE123EF933A15753C1A9659C8B63). *New York Times*. . Retrieved 2007-08-03.

- Erwin Chargaff Papers (http://www.amphilsoc.org/library/mole/c/chargaff.htm), American Philosophical Society

- Chargaff obituary (http://education.guardian.co.uk/higher/medicalscience/story/0,9837,747814,00.html) from *The Guardian*, July 2, 2002

- Watson, James D.; Baker, Tania A.; Bell, Stephen B.; Gann, Alexander; Levine, Michael; & Losick, Richard (2004). *Molecular Biology of the Gene* (5th ed. ed.). Benjamin Cummings. ISBN 0-8053-4635-X.

- The composition of the deoxyribonucleic acid of salmon sperm (http://www.jbc.org/cgi/reprint/192/1/223. pdf) by E. Chargaff, R. Lipshitz, C. Green and M. E. Hodes in *Journal of Biological Chemistry* (1951) volume 192 pages 223-230.

- Watson, James D. (1980) [orig. 1968]. *The Double Helix: A personal account of the discovery of the structure of DNA* (critical edition ed.). Norton. ISBN 0-393-01245-X.

External links

- "How Genetics Got a Chemical Education" (http://crystal.biochem.queensu.ca/forsdyke/bioinfo1.htm). *Annals of the New York Academy of Sciences* (1979), **325**, 345-360.

- (http://www.weizmann.ac.il/ICS/booklet/22/pdf/bob_weintraub.pdf) Weintraub, B. (2006); Erwin Chargaff and Chargaff's Rules. Chemistry in Israel, Bulletin of the Israel Chemical Society. Issue No.22, Sept. 2006. p29-31.

- Key Participants: Erwin Chargaff (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/ people/chargaff.html) - *Linus Pauling and the Race for DNA: A Documentary History*

Raymond Gosling

Raymond Gosling (born 1926) is a distinguished scientist who worked with both Maurice Wilkins and Rosalind Franklin at King's College London in deducing the structure of DNA, under the direction of Sir John Randall. His other KCL colleagues included Alex Stokes and Herbert Wilson.

Early years

He was born in 1926 and attended school in Wembley. He studied physics at University College London from 1944 to 1947 and became a hospital physicist at the King's Fund and Middlesex Hospital between 1947 and 1949 before joining King's College London as a research student.[1]

Professor Raymond Gosling for 2003 "DNA at King's - the continuing story: 50th anniversary of the discovery of the structure of DNA"

Double Helix Discovery

William Astbury

Oswald Avery

Francis Crick

Erwin Chargaff

Max Delbrück

Jerry Donohue

Rosalind Franklin

Raymond Gosling

Phoebus Levene

Linus Pauling

Sir John Randall

Erwin Schrödinger

Alex Stokes

James Watson

Maurice Wilkins

Herbert Wilson

Work at King's and DNA

At King's College London, Gosling worked on X-ray diffraction with Maurice Wilkins, analyzing samples of DNA which they prepared by hydrating and drawing out into thin filaments and photographing in a hydrogen atmosphere.

Gosling was then assigned to Rosalind Franklin when she joined King's College London in 1951. Together they produced the first X-ray diffraction photographs of the "form B" paracrystalline arrays of highly hydrated DNA. She was his academic supervisor. During the next two years, the pair worked closely together to perfect the technique of x-ray diffraction photography of DNA and obtained at the time the sharpest diffraction images of DNA. This work led directly to the 1962 Nobel Prize for Physiology or Medicine being awarded to Francis Crick, James D. Watson and Maurice Wilkins. Gosling was the co-author with Franklin of one of the three papers published in "Nature" in April 1953.[2]

Gosling briefly remained at King's College London following the completion of his thesis in 1954 before lecturing in physics at Queen's College, University of St Andrews, and at the University of the West Indies.[1]

Work at Guy's Hospital

He returned to the UK in 1967 and became Lecturer and Reader at Guy's Hospital Medical School, and Professor and Emeritus Professor in Physics Applied to Medicine from 1984. Here he helped develop the underlying basic medical science and technology for haemodynamic doppler ultrasound vascular assessment in the Non Invasive Angiology Group, and set up the clinical Ultrasonic Angiology Unit.[3] [4] [5] [6]

Gosling has served on numerous committees of the University of London, notably relating to radiological science, and still retains an active professional involvement in medical physics.

See also

- 'Death' of D.N.A. Helix (Crystaline) joke funeral card

References

- Chomet, S. (Ed.), D.N.A. *Genesis of a Discovery*, 1994, Newman- Hemisphere Press, London; NB a few copies are available from Newman-Hemisphere at 101 Swan Court, London SW3 5RY (phone: 07092 060530).
- Wilkins, Maurice, The Third Man of the Double Helix: The Autobiography of Maurice Wilkins ISBN 0-19-860665-6.
- Ridley, Matt; "Francis Crick: Discoverer of the Genetic Code (Eminent Lives)" was first published in July 2006 in the USA and will be then in the UK September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X. [This short book is in the publisher's "Eminent Lives" series.]
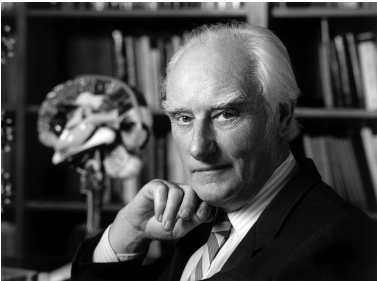
External links

- Raymond Gosling in The King's story [7]
- Images of Doppler-shifted ultrasound units 1974-1981 [8] jointly developed by Dr. B.A.Coghlan and Prof. R.G.Gosling's Blood Flow Group at the Physics Dept., Guy's Hospital Medical School, London. These early devices were used for haemodynamic assessment of normal volunteers and assessment of patients with peripheral vascular disease.

References

[1] "King's College biography" (http://www.kcl.ac.uk/depsta/iss/archives/dna/faq7.html). . Retrieved 2006-11-29.

[2] Wilkins, Maurice (2003). *The third man of the double helix the autobiography of Maurice Wilkins*. Cambridge, Eng: University Press. ISBN
     0-19-860665-6.

[3] Side CD, Gosling RG (30 July 1971). "Non-surgical assessment of cardiac function". *Nature* **232** (5309): 335−6. doi: 10.1038/232335a0
     (http://dx.doi.org/10.1038/232335a0). PMID 5094838 (http://www.ncbi.nlm.nih.gov/pubmed/5094838).

[4] Laogun AA, Gosling RG (August 1982). "In vivo arterial compliance in man". *Clin Phys Physiol Meas* **3** (3): 201−12. doi:
     10.1088/0143-0815/3/3/004 (http://dx.doi.org/10.1088/0143-0815/3/3/004). PMID 7140158 (http://www.ncbi.nlm.nih.gov/pubmed/
     7140158).

[5] Kontis S, Gosling RG (May-Jun 1987). "A computerized method for processing of spectrally analysed Doppler-shifted signals from insonated
     arteries". *J Med Eng Technol* **11** (3): 108−12. doi: 10.3109/03091908709018151 (http://dx.doi.org/10.3109/03091908709018151). PMID
     3305952 (http://www.ncbi.nlm.nih.gov/pubmed/3305952).

[6] Baskett JJ, Lewis RR, Beasley MG, Gosling RG (July 1990). "Changes in carotid artery compliance with age". *Age Ageing* **19** (4): 241−6.
     doi: 10.1093/ageing/19.4.241 (http://dx.doi.org/10.1093/ageing/19.4.241). PMID 2220482 (http://www.ncbi.nlm.nih.gov/pubmed/
     2220482). - Abstract (http://www.iop.org/EJ/abstract/0143-0815/3/3/004)

[7] http://www.kcl.ac.uk/about/history/archives/dna/individuals/gosling.html

[8] https://www.cs.tcd.ie/coghlan/doptst.htm

Francis Crick

Francis Harry Compton Crick	
Francis Harry Compton Crick	
Born	8 June 1916 Weston Favell, Northamptonshire, England
Died	28 July 2004 (aged 88) San Diego, California, U.S. Colon Cancer
Residence	UK, U.S.
Nationality	British
Fields	Molecular biologist, Physicist
Institutions	Institute for the Furtherment of Genetic Studies
Alma mater	University College London University of Cambridge
Doctoral advisor	Max Perutz
Known for	DNA structure, consciousness
Notable awards	Nobel Prize (1962)

Francis Harry Compton Crick OM FRS (8 June 1916 – 28 July 2004), was a British molecular biologist, physicist, and neuroscientist, and most noted for being one of two co-discoverers of the structure of the DNA molecule in 1953, together with James D. Watson. He, James D. Watson and Maurice Wilkins were jointly awarded the 1962 Nobel Prize for Physiology or Medicine "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material" .[1]

Crick is widely known for use of the term "central dogma" to summarise an idea that genetic information flow in cells is essentially one-way, from DNA to RNA to protein. Crick was an important theoretical molecular biologist and played a crucial role in research related to revealing the genetic code.[2]

During the remainder of his career, he held the post of J.W. Kieckhefer Distinguished Research Professor at the Salk Institute for Biological Studies in La Jolla, California. His later research centered on theoretical neurobiology and attempts to advance the scientific study of human consciousness. He remained in this post until his death; "he was editing a manuscript on his death bed, a scientist until the bitter end" said Christof Koch[3] .

Family and Education

Francis Crick, the first son of Harry Crick (1887-1948) and Annie Elizabeth Crick, née Wilkins, (1879-1955). He was born and raised in Weston Favell, then a small village near the English town of Northampton in which Crick's father and uncle ran the family's boot and shoe factory. His grandfather, Walter Drawbridge Crick (1857-1903), an amateur naturalist, wrote a survey of local foraminifera (single-celled protists with shells), corresponded with Charles Darwin[4] , and had two gastropods (snails or slugs) named after him.

At an early age, Francis was attracted to science and what he could learn about it from books. As a child, he was taken to church by his parents, but by about age 12 he told his mother that he no longer wanted to attend, preferring a scientific search for answers over religious belief.[5] He was educated at Northampton Grammar School and, after the age of 14, Mill Hill School in London (on scholarship), where he studied mathematics, physics, and chemistry with his best friend John Shilston. At the age of 21, Crick earned a B.Sc. degree in physics from University College of London (UCL)[6] after he had failed to gain his intended place at a Cambridge college, probably through failing their requirement for Latin; his contemporaries in British DNA research Rosalind Franklin and Maurice Wilkins both went up to Cambridge colleges, to Newnham and St. John's respectively. Crick later became a PhD student and Honorary Fellow of Caius College and mainly worked at the Cavendish Laboratory and the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge. He was also an Honorary Fellow of Churchill College and of University College London.

Crick began a Ph.D. research project on measuring viscosity of water at high temperatures (what he later described as "the dullest problem imaginable"[7]) in the laboratory of physicist Edward Neville da Costa Andrade, but with the outbreak of World War II (in particular, an incident during the Battle of Britain when a bomb fell through the roof of the laboratory and destroyed his experimental apparatus),[8] Crick was deflected from a possible career in physics.

During World War II, he worked for the Admiralty Research Laboratory, from which emerged a group of many notable scientists, including David Bates, Robert Boyd, George Deacon, John Gunn, Harrie Massey and Nevill Mott; he worked on the design of magnetic and acoustic mines and was instrumental in designing a new mine that was effective against German minesweepers.[9]

After World War II, in 1947, Crick began studying biology and became part of an important migration of physical scientists into biology research. This migration was made possible by the newly won influence of physicists such as Sir John Randall, who had helped win the war with inventions such as radar. Crick had to adjust from the "elegance and deep simplicity" of physics to the "elaborate chemical mechanisms that natural selection had evolved over billions of years." He described this transition as, "almost as if one had to be born again." According to Crick, the experience of learning physics had taught him something important—hubris—and the conviction that since physics was already a success, great advances should also be possible in other sciences such as biology. Crick felt that this attitude encouraged him to be more daring than typical biologists who tended to concern themselves with the daunting problems of biology and not the past successes of physics.

For the better part of two years, Crick worked on the physical properties of cytoplasm at Cambridge's Strangeways Laboratory, headed by Honor Bridget Fell, with a Medical Research Council studentship, until he joined Max Perutz and John Kendrew at the Cavendish Laboratory. The Cavendish Laboratory at Cambridge was under the general direction of Sir Lawrence Bragg, who won the Nobel Prize in 1915 at the age of 25. Bragg was influential in the effort to beat a leading American chemist, Linus Pauling, to the discovery of DNA's structure (after having been 'pipped-at-the-post' by Pauling's success in determining the alpha helix structure of proteins). At the same time Bragg's Cavendish Laboratory was also effectively competing with King's College London, whose Biophysics department was under the direction of Sir John Randall. (Randall had turned down Francis Crick from working at King's College.) Francis Crick and Maurice Wilkins of King's College were personal friends, which influenced subsequent scientific events as much as the close friendship between Crick and James Watson. Crick and Wilkins first met at King's College and not, as erroneously recorded by two authors, at the Admiralty during World War II.

He married twice, was father to three children and grandfather to six grandchildren; his brother Anthony (born in 1918) predeceased him in 1966:

- Spouses: Ruth Doreen Crick, née Dodd (b. 1913, m. 18 February 1940 – 8 May 1947); Odile Crick, née Speed (b. 11 August 1920, m. 14 August 1949 – 28 July 2004, d. 5 July 2007)
- Children: Michael Francis Compton (b. 25 November 1940) [by Doreen Crick]; Gabrielle Anne (b. 15 July 1951) and Jacqueline Marie-Therese [later Nichols] (b. 12 March 1954) [by Odile Crick];
- Grandchildren: Alex (b. March 1974), Kindra (b. May 1976), Camberley (b. June 1978), and Francis (b. February 1981), Michael & Barbara Crick's children; Mark & Nicholas, Jacqueline and Christopher Nichols' stepchildren.

Crick died of colon cancer on 28 July 2004 at the University of California San Diego (UCSD) Thornton Hospital in La Jolla]; he was cremated and his ashes were scattered into the Pacific Ocean. A public memorial was held on 27th of September 2004 at The Salk Institute, La Jolla, near San Diego, California; guest speakers included James D. Watson, Sydney Brenner, Alex Rich, the late Seymour Benzer, Aaron Klug, Christof Koch, Pat Churchland, Vilayanur Ramachandran, Tomaso Poggio, the late Leslie Orgel, Terry Sejnowski, his son Michael Crick, and his youngest daughter Jacqueline Nichols.[10] A more private memorial for his family and colleagues was also held on 3rd of August 2004.

Biology research

Francis Crick
Discovery of the DNA Double Helix

Francis Crick, lecturing ca. 1979

William Astbury	Oswald Avery
Francis Crick	Erwin Chargaff
Jerry Donohue	Rosalind Franklin
Phoebus Levene	Linus Pauling
Erwin Schrödinger	Alec Stokes
James Watson	Maurice Wilkins

Crick was interested in two fundamental unsolved problems of biology. First, how molecules make the transition from the non-living to the living, and second, how the brain makes a conscious mind.[11] He realized that his background made him more qualified for research on the first topic and the field of biophysics. It was at this time of Crick's transition from physics into biology that he was influenced by both Linus Pauling and Erwin Schrödinger.[12] It was clear in theory that covalent bonds in biological molecules could provide the structural stability needed to hold genetic information in cells. It only remained as an exercise of experimental biology to discover exactly which molecule was the genetic molecule.[13] [14] In Crick's view, Charles Darwin's theory of evolution by natural selection, Gregor Mendel's genetics and knowledge of the molecular basis of genetics, when combined, revealed the secret of life.[15]

It was clear that some macromolecule such as protein was likely to be the genetic molecule.[16] However, it was well-known that proteins are structural and functional macromolecules, some of which carry out enzymatic reactions of cells.[16] In the 1940s, some evidence had been found pointing to another macromolecule, DNA, the other major component of chromosomes, as a candidate genetic molecule. In the 1944 Avery-MacLeod-McCarty experiment, Oswald Avery and his collaborators showed that a heritable phenotypic difference could be caused in bacteria by providing them with a particular DNA molecule.[14]
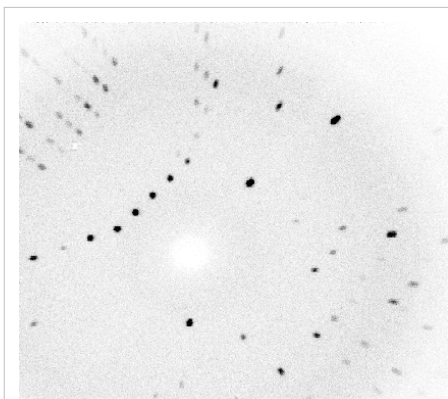
An X-ray diffraction image for the protein myoglobin. At the time when Crick participated in the discovery of the DNA Double Helix, he was doing his thesis research on X-ray diffraction analysis of protein structure (see below).

However, other evidence was interpreted as suggesting that DNA was structurally uninteresting and possibly just a molecular scaffold for the apparently more interesting protein molecules.[17] Crick was in the right place, in the right frame of mind, at the right time (1949), to join Max Perutz's project at Cambridge University, and he began to work on the X-ray crystallography of proteins.[18] X-ray crystallography theoretically offered the opportunity to reveal the molecular structure of large molecules like proteins and DNA, but there were serious technical problems then preventing X-ray crystallography from being applicable to such large molecules.[18]

1949–1950

Crick taught himself the mathematical theory of X-ray crystallography.[19] During the period of Crick's study of X-ray diffraction, researchers in the Cambridge lab were attempting to determine the most stable helical conformation of amino acid chains in proteins (the α helix). Linus Pauling was the first to identify[20] the 3.6 amino acids per helix turn ratio of the α helix. Crick was witness to the kinds of errors that his co-workers made in their failed attempts to make a correct molecular model of the α helix; these turned out to be important lessons that could be applied, in the future, to the helical structure of DNA. For example, he learned[21] the importance of the structural rigidity that double bonds confer on molecular structures which is relevant both to peptide bonds in proteins and the structure of nucleotides in DNA.

1951–1953: DNA structure

In 1951, together with William Gemmell Cochran and V. Vand, Crick assisted in the development of a mathematical theory of X-ray diffraction by a helical molecule.[22] This theoretical result matched well with X-ray data obtained for proteins that contain sequences of amino acids in the Alpha helix conformation (published in *Nature* in 1952).[23] Helical diffraction theory turned out to also be useful for understanding the structure of DNA.

Late in 1951, Crick started working with Tevin D. Edwards at Cavendish Laboratory at the University of Cambridge, England. Using "Photo 51" (the X-ray diffraction results of Raymond Gosling and Rosalind Franklin of King's College London, given to them by Gosling and Franklin's colleague Maurice Wilkins), Watson and Crick together developed a model for a helical structure of DNA, which they published in 1953.[24] For this and subsequent work they were jointly awarded the Nobel Prize in Physiology or Medicine in 1962 with Maurice Wilkins.[25]

When James Watson came to Cambridge, Crick was a 35-year-old post-graduate student (due to his work during WWII) and Watson was only 23, but he already had a Ph.D. They shared an interest in the fundamental

Francis Crick's first sketch of the deoxyribonucleic acid double-helix pattern

problem of learning how genetic information might be stored in molecular form.[26] [27] Watson and Crick talked endlessly about DNA and the idea that it might be possible to guess a good molecular model of its structure.[13] A key piece of experimentally-derived information came from X-ray diffraction images that had been obtained by Maurice Wilkins, Rosalind Franklin, and their research student, Raymond Gosling. In November 1951, Wilkins came to Cambridge and shared his data with Watson and Crick. Alexander Stokes (another expert in helical diffraction theory) and Wilkins (both at King's College) had reached the conclusion that X-ray diffraction data for DNA indicated that the molecule had a helical structure—but Franklin vehemently disputed this conclusion. Stimulated by their discussions with Wilkins and what Watson learned by attending a talk given by Franklin about her work on DNA, Crick and Watson produced and showed off an erroneous first model of DNA. Their hurry to produce a model of DNA structure was driven in part by Watson's belief that they were competing against Linus Pauling. Given Pauling's recent success in discovering the Alpha helix, it was not unreasonable to worry that Pauling might also be the first to determine the structure of DNA.[28]

Many have speculated about what might have happened had Pauling been able to travel to Britain as planned in May 1952.[29] He *might* have been invited to see some of the Wilkins/Franklin X-ray diffraction data, and such an event *might* have led him to a double helix model (which remains—as said above—total speculation). As it was, his political activities caused his travel to be restricted by the U. S. government and he did not visit the UK until later, at which point he met none of the DNA researchers in England—but at any rate he was preoccupied with proteins at the time, not DNA.[29] [30] Watson and Crick were not officially working on DNA. Crick was writing his Ph.D. thesis; Watson also had other work such as trying to obtain crystals of myoglobin for X-ray diffraction experiments. In 1952, Watson did X-ray diffraction on tobacco mosaic virus and found results indicating that it had helical structure. Having failed once, Watson and Crick were now somewhat reluctant to try again and for a while they were forbidden to make further efforts to find a molecular model of DNA.
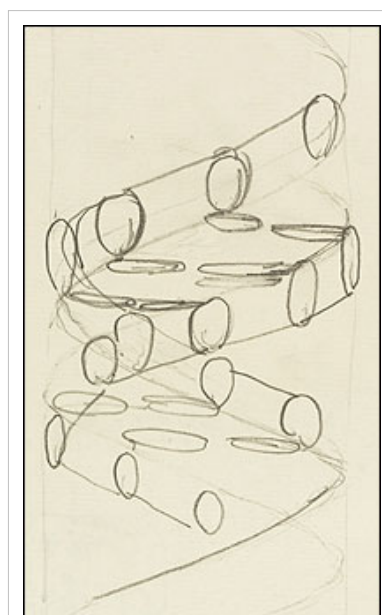
Of great importance to the model building effort of Watson and Crick was Rosalind Franklin's understanding of basic chemistry, which indicated that the hydrophilic phosphate-containing backbones of the nucleotide chains of DNA should be positioned so as to interact with water molecules on the outside of the molecule while the hydrophobic bases should be packed into the core. Franklin shared this chemical knowledge with Watson and Crick when she pointed out to them that their first model (from 1951, with the phosphates inside) was obviously wrong.

Crick described what he saw as the failure of Maurice Wilkins and Rosalind Franklin to cooperate and work towards finding a molecular model of DNA as a major reason why he and Watson eventually made a second attempt to do so. They asked for, and received, permission to do so from both William Lawrence Bragg and Wilkins. In order to construct their model of DNA, Watson and Crick made use of information from unpublished X-ray diffraction images of Franklin's (shown at meetings and freely shared by Wilkins), including preliminary accounts of Franklin's results/photographs of the X-ray images that were included in a written progress report for the King's College laboratory of Sir John Randall from late 1952.

Diagram that emphasizes the phosphate backbone of DNA. Watson and Crick first made helical models with the phosphates at the center of the helices.

It is a matter of debate whether Watson and Crick should have had access to Franklin's results without her knowledge or permission, and before she had a chance to formally publish the results of her detailed analysis of her X-ray diffraction data which were included in the progress report. However, Watson and Crick found fault in her steadfast assertion that, according to her data, a helical structure was not the only possible shape for DNA—so they had a dilemma. In an effort to clarify this issue, Max Ferdinand Perutz later published what had been in the progress report, [31] and suggested that nothing was in the report that Franklin herself had not said in her talk (attended by Watson) in late 1951. Further, Perutz explained that the report was to a Medical Research Council (MRC) committee that had been created in order to "establish contact between the different groups of people working for the Council". Randall's and Perutz's laboratories were both funded by the MRC.

It is also not clear how important Franklin's unpublished results from the progress report actually were for the model-building done by Watson and Crick. After the first crude X-ray diffraction images of DNA were collected in the 1930s, William Astbury had talked about stacks of nucleotides spaced at 3.4 angström (0.34 nanometre) intervals in DNA. A citation to Astbury's earlier X-ray diffraction work was one of only eight references in Franklin's first paper on DNA.[32] Analysis of Astbury's published DNA results and the better X-ray diffraction images collected by Wilkins and Franklin revealed the helical nature of DNA. It was possible to predict the number of bases stacked within a single turn of the DNA helix (10 per turn; a full turn of the helix is 27 angströms [2.7 nm] in the compact A form, 34 angströms [3.4 nm] in the wetter B form). Wilkins shared this information about the B form of DNA with Crick and Watson. Crick did not see Franklin's B form X-ray images (Photo 51) until after the DNA double helix model was published.[33]

One of the few references cited by Watson and Crick when they published their model of DNA, was to a published article that included Sven Furberg's DNA model that had the bases on the inside. Thus, the Watson and Crick model was not the first "bases in" model to be published. Furberg's results had also provided the correct orientation of the DNA sugars with respect to the bases. During their model building, Crick and Watson learned that an anti-parallel orientation of the two nucleotide chain backbones worked best to orient the base pairs in the centre of a double helix. Crick's access to Franklin's progress report of late 1952 is what made Crick confident that DNA was a double helix
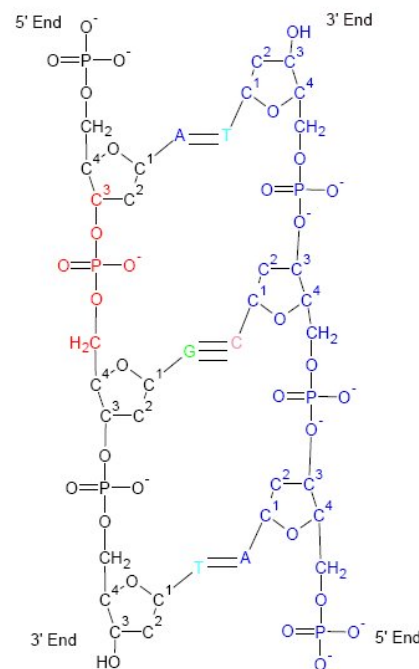
with anti-parallel chains, but there were other chains of reasoning and sources of information that also led to these conclusions.[34]

As a result of leaving King's College for another institution, Franklin was asked by John Randall to give up her work on DNA. When it became clear to Wilkins and the supervisors of Watson and Crick that Franklin was going to the new job, and that Linus Pauling was working on the structure of DNA, they were willing to share Franklin's data with Watson and Crick, in the hope that they could find a good model of DNA before Pauling was able. Franklin's X-ray diffraction data for DNA and her systematic analysis of DNA's structural features was useful to Watson and Crick in guiding them towards a correct molecular model. The key problem for Watson and Crick, which could not be resolved by the data from King's College, was to guess how the nucleotide bases pack into the core of the DNA double helix.

Another key to finding the correct structure of DNA was the so-called Chargaff ratios, experimentally determined ratios of the nucleotide subunits of DNA: the amount of guanine is equal to cytosine and the amount of adenine is equal to thymine. A visit by Erwin Chargaff to England in 1952 reinforced the salience of this important fact for Watson and Crick. The significance of these ratios for the structure of DNA were not recognized until Watson, persisting in building structural models, realized that A:T and C:G pairs are structurally similar. In particular, the length of each base pair is the same. The base pairs are held together by hydrogen bonds, the same non-covalent interaction that stabilizes the protein α-helix. Watson's recognition of the A:T and C:G pairs was aided by information from Jerry Donohue about the most likely structures of the nucleobases.[35] After the discovery of the hydrogen bonded A:T and C:G pairs, Watson and Crick soon had their double helix model of DNA with the hydrogen bonds at the core of the helix providing a way to "unzip" the two complementary strands for easy replication: the last key requirement for a likely model of the genetic molecule. As important as Crick's contributions to the discovery of the double helical DNA model were,

Diagrammatic representation of some key structural features of DNA. The similar structures of guanine:cytosine and adenine:thymine base pairs is illustrated. The base pairs are held together by hydrogen bonds. The phosphate backbones are anti-parallel.

he stated that without the chance to collaborate with Watson, he would not have found the structure by himself.[36]
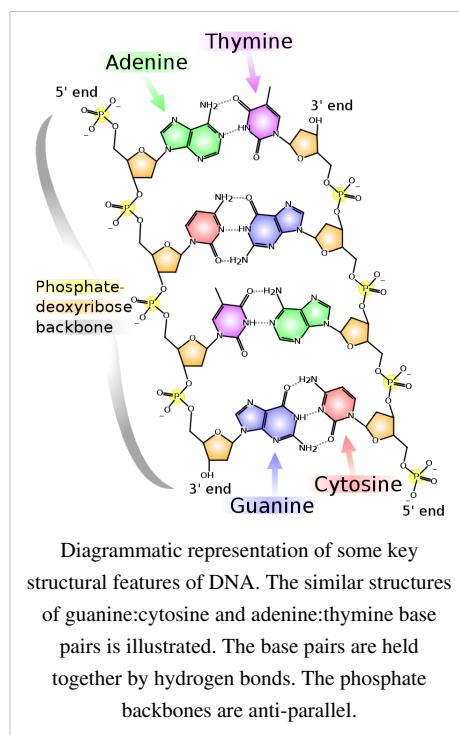
Crick did tentatively attempt to perform some experiments on nucleotide base pairing, but he was more of a theoretical than an experimental biologist. There was another near-discovery of the base pairing rules in early 1952. Crick had started to think about interactions between the bases. He asked John Griffith to try to calculate attractive interactions between the DNA bases from chemical principles and quantum mechanics. Griffith's best guess was that A:T and G:C were attractive pairs. At that time, Crick was not aware of Chargaff's rules and he made little of Griffith's calculations, although it did start him thinking about complementary replication. Identification of the correct base-pairing rules (A-T, G-C) was achieved by Watson "playing" with cardboard cut-out models of the nucleotide bases, much in the manner that Linus Pauling had discovered the protein alpha helix a few years earlier. The Watson and Crick discovery of the DNA double helix structure was made possible by their willingness to combine theory, modeling and experimental results (albeit mostly done by others) to achieve their goal .

The discovery was made on February 28, 1953; the first Watson/Crick paper appeared in Nature on April 25, 1953. Sir Lawrence Bragg, the director of the Cavendish Laboratory, where Watson and Crick worked, gave a talk at Guys Hospital Medical School in London on Thursday, May 14, 1953 which resulted in an article by Ritchie Calder in The News Chronicle of London, on Friday, May 15, 1953, entitled "Why You Are You. Nearer Secret of Life." The news reached readers of The New York Times the next day; Victor K. McElheny, in researching his biography, "Watson and DNA: Making a Scientific Revolution", found a clipping of a six-paragraph New York Times article written

from London and dated May 16, 1953 with the headline "Form of `Life Unit' in Cell Is Scanned." The article ran in an early edition and was then pulled to make space for news deemed more important. (The New York Times subsequently ran a longer article on June 12, 1953). The Cambridge University undergraduate newspaper *Varsity* also ran its own short article on the discovery on Saturday, May 30, 1953. Bragg's original announcement of the discovery at a Solvay conference on proteins in Belgium on 8 April 1953 went unreported by the British press!

Molecular biology

In 1954, at the age of 37, Crick completed his Ph.D. thesis: "X-Ray Diffraction: Polypeptides and Proteins" and received his degree. Crick then worked in the laboratory of David Harker at Brooklyn Polytechnic Institute, where he continued to develop his skills in the analysis of X-ray diffraction data for proteins, working primarily on ribonuclease and the mechanisms of protein synthesis. David Harker, the American X-ray crystallographer, was described as "the John Wayne of crystallography" by Vittorio Luzzati, a crystallographer at the Centre for Molecular Genetics in Gif-sur-Yvette near Paris, who had worked with Rosalind Franklin.

After the discovery of the double helix model of DNA, Crick's interests quickly turned to the biological implications of the structure. In 1953, Watson and Crick published another article in *Nature* which stated: "it therefore seems likely that the precise sequence of the bases is the code that carries the genetical information".[38]

Crick and Watson DNA model built in 1953, was reconstructed [37] largely from its original pieces in 1973 and donated to the National Science Museum in London.
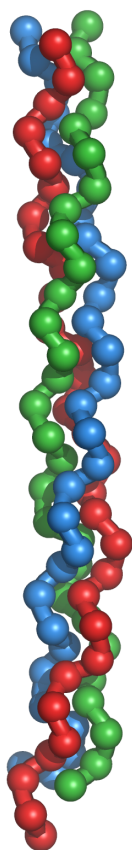
In 1956, Crick and Watson speculated on the structure of small viruses. They suggested that spherical viruses such as Tomato bushy stunt virus had icosahedral symmetry and were made from 60 identical subunits.[39]

After his short time in New York, Crick returned to Cambridge where he worked until 1976, at which time he moved to California. Crick engaged in several X-ray diffraction collaborations such as one with Alexander Rich on the structure of collagen.[40] However, Crick was quickly drifting away from continued work related to his expertise in the interpretation of X-ray diffraction patterns of proteins.

George Gamow established a group of scientists interested in the role of RNA as an intermediary between DNA as the genetic storage molecule in the nucleus of cells and the synthesis of proteins in the cytoplasm. It was clear to Crick that there had to be a code by which a short sequence of nucleotides would specify a particular amino acid in a newly synthesized protein. In 1956, Crick wrote an informal paper about the genetic coding problem for the small group of scientists in Gamow's RNA group.[41] In this article, Crick reviewed the evidence supporting the idea that there was a common set of about 20 amino acids used to synthesize proteins. Crick proposed that there was a corresponding set of small "adaptor molecules" that would hydrogen bond to short sequences of a nucleic acid, and also link to one of the amino acids. He also explored the many theoretical possibilities by which short nucleic acid sequences might code for the 20 amino acids.
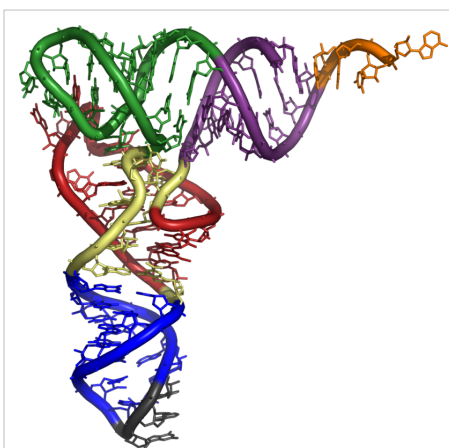
Collagen triple helix.

During the mid-to-late 1950s Crick was very much intellectually engaged in sorting out the mystery of how proteins are synthesized. By 1958, Crick's thinking had matured and he could list in an orderly way all of the key features of the protein synthesis process:[42]

- genetic information stored in the sequence of DNA molecules
- a "messenger" RNA molecule to carry the instructions for making one protein to the cytoplasm
- adaptor molecules ("they might contain nucleotides") to match short sequences of nucleotides in the RNA messenger molecules to specific amino acids
- ribonucleic-protein complexes that catalyse the assembly of amino acids into proteins according to the messenger RNA

The adaptor molecules were eventually shown to be tRNAs and the catalytic "ribonucleic-protein complexes" became known as ribosomes.

Molecular model of a tRNA molecule. Crick predicted that such adaptor molecules might exist as the links between codons and amino acids.

An important step was later realization (in 1960) that the messenger RNA was not the same as the ribosomal RNA. None of this, however, answered the fundamental theoretical question of the exact nature of the genetic code. In his 1958 article, Crick speculated, as had others, that a triplet of nucleotides could code for an amino acid. Such a code might be "degenerate", with 4×4×4=64 possible triplets of the four nucleotide subunits while there were only 20 amino acids. Some amino acids might have multiple triplet codes.

Crick also explored other codes in which, for various reasons, only some of the triplets were used, "magically" producing just the 20 needed combinations. Experimental results were needed; theory alone could not decide the nature of the code. Crick also used the term "central dogma" to summarize an idea that implies that genetic information flow between macromolecules would be essentially one-way:

DNA → RNA → Protein

Some critics thought that by using the word "dogma", Crick was implying that this was a rule that could not be questioned, but all he really meant was that it was a compelling idea without much solid evidence to support it. In his thinking about the biological processes linking DNA genes to proteins, Crick made explicit the distinction between the materials involved, the energy required, and the information flow. Crick was focused on this third component (information) and it became the organizing principle of what became known as molecular biology. Crick had by this time become a highly influential theoretical molecular biologist.

Proof that the genetic code is a degenerate triplet code finally came from genetics experiments, some of which were performed by Crick.[43] The details of the code came mostly from work by Marshall Nirenberg and others who synthesized synthetic RNA molecules and used them as templates for *in vitro* protein synthesis.[44]

Controversy about using King's College London's results

An enduring controversy has been generated by Watson and Crick's use of DNA X-ray diffraction data collected by Rosalind Franklin and her student Raymond Gosling. The controversy arose from the fact that some of the data were shown to them, without her knowledge, by Maurice Wilkins and Max Perutz.[45] Her experimental results provided estimates of the water content of DNA crystals, and these results were most consistent with the three sugar-phosphate backbones being on the outside of the molecule.[46] Franklin personally told Crick and Watson that the backbones had to be on the outside, whilst vehemently stating that her data did not force one to conclude that DNA has a helical structure. Her identification of the space group for DNA crystals revealed to Crick that the DNA strands were antiparallel, which helped Watson and Crick decide to look for DNA models with two antiparallel polynucleotide strands. The X-ray diffraction images collected by Franklin provided the best evidence for the helical nature of DNA—but she failed to recognise this fact. However Franklin's experimental work proved important in Crick and Watson's development of the correct model.

Prior to publication of the double helix structure, Watson and Crick had little interaction with Franklin. Crick and Watson felt that they had benefited from collaborating with Maurice Wilkins. They offered him a co-authorship on the article that first described the double helix structure of DNA. Wilkins turned down the offer, and was in part responsible for the terse character of the acknowledgment of experimental work done at King's College London. Rather than make any of the DNA researchers at King's College co-authors on the Watson and Crick double helix article, the solution was to publish two additional papers from King's College along with the helix paper. Brenda Maddox suggested that because of the importance of her experimental results in Watson and Crick's model building and theoretical analysis, Franklin should have had her name on the original Watson and Crick paper in *Nature*.[47] Franklin and Gosling submitted their own joint 'second' paper to *Nature* at the same time as Wilkins, Stokes, and Wilson submitted theirs (i.e. the 'third' paper on DNA).

Views on religion

Crick once joked, "Christianity may be OK between consenting adults in private but should not be taught to young children."[48]

In his book *Of Molecules and Men*, Crick expressed his views on the relationship between science and religion.[49] After suggesting that it would become possible for people to wonder if a computer might be programmed so as to have a soul, he wondered: at what point during biological evolution did the first organism have a soul? At what moment does a baby get a soul? Crick stated his view that the idea of a non-material soul that could enter a body and then persist after death is just that, an imagined idea. For Crick, the mind is a product of physical brain activity and the brain had evolved by natural means over millions of years. Crick felt that it was important that evolution by natural selection be taught in public schools and that it was regrettable that English schools had compulsory religious instruction. Crick felt that a new scientific world view was rapidly being established, and predicted that once the detailed workings of the brain were eventually revealed, erroneous Christian concepts about the nature of humans and the world would no longer be tenable; traditional conceptions of the "soul" would be replaced by a new understanding of the physical basis of mind. He was sceptical of organized religion, referring to himself as a sceptic and an agnostic with "a strong inclination towards atheism".[50]

In 1960, Crick accepted a fellowship at Churchill College Cambridge, one factor being that the new college did not have a chapel. Sometime later a large donation was made to establish a chapel and the fellowship elected to accept it. Crick resigned his fellowship in protest.[51]

In October 1969, Crick participated in a celebration of the 100th year of the journal *Nature*. Crick attempted to make some predictions about what the next 30 years would hold for molecular biology. His speculations were later published in *Nature*.[52] Near the end of the article, Crick briefly mentioned the search for life on other planets, but he held little hope that extraterrestrial life would be found by the year 2000. He also discussed what he described as a possible new direction for research, what he called "biochemical theology". Crick wrote, "So many people pray that one finds it hard to believe that they do not get some satisfaction from it".

Crick suggested that it might be possible to find chemical changes in the brain that were molecular correlates of the act of prayer. He speculated that there might be a detectable change in the level of some neurotransmitter or neurohormone when people pray. Crick may have been imagining substances such as dopamine that are released by the brain under certain conditions and produce rewarding sensations. Crick's suggestion that there might someday be a new science of "biochemical theology" seems to have been realized under an alternative name: there is now the new field of neurotheology.[53] Crick's view of the relationship between science and religion continued to play a role in his work as he made the transition from molecular biology research into theoretical neuroscience.

In a book entitled *Life Itself: Its Origin and Nature* (page 88), Crick wrote: "An honest man, armed with all the knowledge available to us now, could only state that in some sense, the origin of life appears at the moment to be almost a miracle, so many are the conditions which would have had to have been satisfied to get it going."
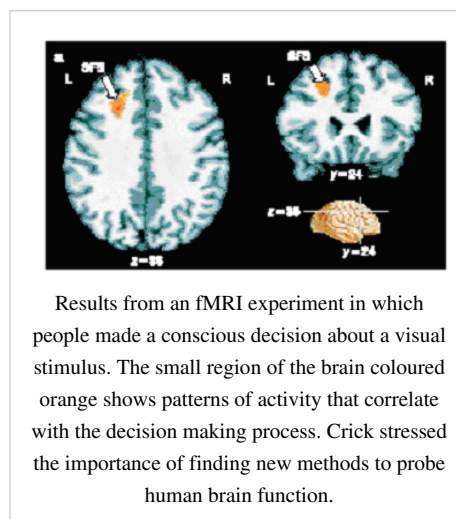
Directed panspermia

During the 1960s, Crick became concerned with the origins of the genetic code. In 1966, Crick took the place of Leslie Orgel at a meeting where Orgel was to talk about the origin of life. Crick speculated about possible stages by which an initially simple code with a few amino acid types might have evolved into the more complex code used by existing organisms.[54] At that time, everyone thought of proteins as the only kind of enzymes and ribozymes had not yet been found. Many molecular biologists were puzzled by the problem of the origin of a protein replicating system that is as complex as that which exists in organisms currently inhabiting Earth. In the early 1970s, Crick and Orgel further speculated about the possibility that the production of living systems from molecules may have been a very rare event in the universe, but once it had developed it could be spread by intelligent life forms using space travel technology, a process they called "Directed Panspermia".[55] In a retrospective article,[56] Crick and Orgel noted that

they had been overly pessimistic about the chances of abiogenesis on Earth when they had assumed that some kind of self-replicating protein system was the molecular origin of life.

Crick addressed the Origin of Protein Synthesis in a paper with Sydney Brenner, Aaron Klug.[57] In this paper, they speculate that code constraints on nucleotide sequences allow protein synthesis without the need for a ribosome. It, however, requires a five base binding between the mRNA and tRNA with a flip of the anti-codon creating a triplet coding, even though it is a five base physical interaction. Thomas H. Jukes pointed out that the code constraints on the mRNA sequence required for this translation mechanism is still preserved.

Neuroscience, other interests

Crick's period at Cambridge was the pinnacle of his long scientific career, but he left Cambridge in 1977 after 30 years, having been offered (and having refused) the Mastership of Gonville & Caius. James Watson claimed at a Cambridge conference marking the 50th anniversary of the discovery of the structure of DNA in 2003: "Now perhaps it's a pretty well kept secret that one of the most uninspiring acts of Cambridge University over this past century was to turn down Francis Crick when he applied to be the Professor of Genetics, in 1958. Now there may have been a series of arguments, which lead them to reject Francis. It was really saying, don't push us to the frontier." The apparently "pretty well kept secret" had already been recorded in Soraya De Chadarevian's "Designs For Life: Molecular Biology After World War II", published by CUP in 2002. His major contribution to molecular biology in Cambridge is well documented in The History of

Results from an fMRI experiment in which people made a conscious decision about a visual stimulus. The small region of the brain coloured orange shows patterns of activity that correlate with the decision making process. Crick stressed the importance of finding new methods to probe human brain function.

the University of Cambridge: Volume 4 (1870 to 1990), which was published by Cambridge University Press in 1992.

According to the University of Cambridge's genetics department official website [58], the electors of the professorship could not reach consensus, prompting the intervention of then University Vice-Chancellor Lord Adrian. Lord Adrian first offered the professorship to a compromise candidate, Guido Pontecorvo, who refused, and is said to have offered it then to Crick, who also refused.

In 1976, Crick took a sabbatical year at the Salk Institute for Biological Studies in La Jolla, California. Crick had been a nonresident fellow of the Institute since 1960. Crick wrote, "I felt at home in Southern California."[59] After the sabbatical, Crick left Cambridge in order to continue working at the Salk Institute. He was also a professor at the University of California, San Diego. He taught himself neuroanatomy and studied many other areas of neuroscience research. It took him several years to disengage from molecular biology because exciting discoveries continued to be made, including the discovery of alternative splicing and the discovery of restriction enzymes, which helped make possible genetic engineering. Eventually, in the 1980s, Crick was able to devote his full attention to his other interest, consciousness. His autobiographical book, *What Mad Pursuit*, includes a description of why he left molecular biology and switched to neuroscience.

Upon taking up work in theoretical neuroscience, Crick was struck by several things:

- there were many isolated subdisciplines within neuroscience with little contact between them
- many people who were interested in behaviour treated the brain as a black box
- consciousness was viewed as a taboo subject by many neurobiologists

Crick hoped he might aid progress in neuroscience by promoting constructive interactions between specialists from the many different subdisciplines concerned with consciousness. He even collaborated with neurophilosophers such as Patricia Churchland. In 1983, as a result of their studies of computer models of neural networks, Crick and

Mitchison proposed that the function of REM sleep is to remove certain modes of interactions in networks of cells in the mammalian cerebral cortex; they called this hypothetical process 'reverse learning' or 'unlearning'. In the final phase of his career, Crick established a collaboration with Christof Koch that lead to publication of a series of articles on consciousness during the period spanning from 1990[60] to 2005. Crick made the strategic decision to focus his theoretical investigation of consciousness on how the brain generates visual awareness within a few hundred milliseconds of viewing a scene. Crick and Koch proposed that consciousness seems so mysterious because it involves very short-term memory processes that are as yet poorly understood. Crick also published a book describing how neurobiology had reached a mature enough stage so that consciousness could be the subject of a unified effort to study it at the molecular, cellular and behavioural levels.[61] Crick's book *The Astonishing Hypothesis* made the argument that neuroscience now had the tools required to begin a scientific study of how brains produce conscious experiences. Crick was skeptical about the value of computational models of mental function that are not based on details about brain structure and function.

Reactions to Crick and his work

Crick has widely been described as talkative, brash, and lacking modesty.[62] His personality combined with his scientific accomplishments produced many opportunities for Crick to stimulate reactions from others, both inside and outside of the scientific world, which was the centre of his intellectual and professional life.[63] Crick spoke rapidly, and rather loudly, and had an infectious and reverberating laugh, and a lively sense of humour. One colleague from the Salk Institute described him as "a brainstorming intellectual powerhouse with a mischievous smile.... Francis was never mean-spirited, just incisive. He detected microscopic flaws in logic. In a room full of smart scientists, Francis continually rearned his position as the heavyweight champ."[64]

Eugenics

Crick occasionally expressed his views on eugenics, usually in private letters. For example, Crick advocated a form of positive eugenics in which wealthy parents would be encouraged to have more children.[65] He once remarked, "In the long run, it is unavoidable that society will begin to worry about the character of the next generation... It is not a subject at the moment which we can tackle easily because people have so many religious beliefs and until we have a more uniform view of ourselves I think it would be risky to try and do anything in the way of eugenics... I would be astonished if, in the next 100 or 200 years, society did not come round to the view that they would have to try to improve the next generation in some extent or one way or another."

Creationism

It has been suggested by some observers that Crick's speculation about panspermia "fits neatly into the intelligent design concept."[66] Crick's name was raised in this context in the Kitzmiller v. Dover Area School District trial over the teaching of intelligent design. Crick was, however, a firm critic of Young earth creationism. In the 1987 United States Supreme Court case Edwards v. Aguillard, Crick joined a group of other Nobel laureates who advised that, "'Creation-science' simply has no place in the public-school science classroom."[67] Crick was also an advocate for the establishment of Darwin Day as a British national holiday.[68]

Recognition

In addition to his third share of the 1962 Nobel prize for Physiology or Medicine, he received many awards and honours, including the Royal and Copley medals of the Royal Society (1972 and 1975), and also the Order of Merit (on November 27, 1991); he refused an offer of a CBE in 1963 and later refused an offer of a knighthood, but was often referred to in error as 'Sir Francis Crick' and even on occasions as 'Lord Crick'; Richard Lewontin's review of *The Double Helix* by James Watson in "The Chicago Sunday Times" on February 25, 1968 contained an astonishing four references to "Sir Francis Crick" - in error. This mistake is being repeated to the present day.

On Saturday, October 20, 1962 the award of Nobel prizes to John Kendrew and Max Perutz, and to Crick, Watson, and Wilkins was satirised in a short sketch in the BBC TV programme That Was The Week That Was with the Nobel Prizes being referred to as 'The Alfred Nobel Peace Pools.'

The Francis Crick Prize Lectures at The Royal Society, London

The Francis Crick Lecture was established in 2003 following an endowment by his former colleague, Sydney Brenner, joint winner of the 2002 Nobel Prize in Physiology and Medicine.[69] The lecture is delivered annually in any field of biological sciences, with preference given to the areas in which Francis Crick himself worked. Importantly, the lectureship is aimed at younger scientists, ideally under 40, or whose career progression corresponds to this age.

Stained glass window in the dining hall of Caius College, in Cambridge, commemorating Francis Crick and representing the structure of DNA.

The Francis Crick Graduate Lectures at the University of Cambridge

The University of Cambridge Graduate School of Biological, Medical and Veterinary Sciences hosts The Francis Crick Graduate Lectures. The first two lectures were by John Gurdon and Tim Hunt.[70] [71]

"For my generation, Francis Crick was probably the most obviously influential presence. He was often at lunch in the canteen of the Laboratory of Molecular Biology where he liked to explain what he was thinking about, and he was always careful to make sure that everyone round the table really understood. He was a frequent presence at talks in and around Cambridge, where he liked to ask questions. Sometimes, I remember thinking, they seemed slightly ignorant questions to which a man of his extraordinary range and ability ought to have known the answers. Only slowly did it dawn on me that he only and always asked questions when he was unclear or unsure, a great lesson." (Tim Hunt, first Francis Crick Graduate Lecturer: June 2005)

The wording on the new DNA sculpture (which was donated by James Watson) outside Clare College's Thirkill Court, Cambridge, England is

a) on the base:

i) "These strands unravel during cell reproduction. Genes are encoded in the sequence of bases."

ii) "The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins."

b) on the helices:

i) "The structure of DNA was discovered in 1953 by Francis Crick and James Watson while Watson lived here at Clare."

ii) "The molecule of DNA has two helical strands that are linked by base pairs Adenine - Thymine or Guanine - Cytosine."

The aluminium sculpture stands fifteen feet high. It took a pair of technicians a fortnight to build it. For the artist responsible it was an opportunity to create a monument that brings together the themes of science and nature; Charles Jencks, Sculptor said "It embraces the trees, you can sit on it and the ground grows up and it twists out of the ground. So it's truly interacting with living things like the turf, and that idea was behind it and I think it does celebrate life and DNA." Tony Badger, Master of Clare, said: "It is wonderful to have this lasting reminder of his achievements while he* was at Clare and the enormous contribution he* and Francis Crick have made to our understanding of life on earth." * James D. Watson.

[72] Westminster City Council unveiled a green plaque to Francis Crick on the front façade of 56 St George's Square, Pimlico, London SW1 on the 20 June 2007; Crick lived in the first floor flat, together with Robert Dougall of BBC radio and later TV fame, a former Royal Navy associate.; Robert Dougall had replaced Georg Kreisel who left the flat in 1946.

Crick was elected a fellow of CSICOP in 1983 and a Humanist Laureate of the International Academy of Humanism in the same year. In 1995, Francis Crick was one of the original endorsers of the Ashley Montagu Resolution to petition for an end to the genital mutilation of children.

Another sculpture entitled *Discovery*, was installed on Tuesday,13 December 2005 and a formal ribbon-cutting ceremony was held on Thursday, 15 December 2005 at 11.00am in Abington Street, Northampton. According to the late Mr Lynn Wilson, chairman of the Wilson Foundation, "The sculpture celebrates the life of a world class scientist who must surely be considered the greatest Northamptonian of all time - by discovering DNA he unlocked the whole future of genetics and the alphabet of life."

- Fellow of the Royal Society
- Fellow International Academy of Humanism
- Fellow CSICOP

Books by Francis Crick

- *Of Molecules and Men* (Prometheus Books, 2004; original edition 1967) ISBN 1-59102-185-5
- *Life Itself* (Simon & Schuster, 1981) ISBN 0-671-25562-2
- *What Mad Pursuit: A Personal View of Scientific Discovery* (Basic Books reprint edition, 1990) ISBN 0-465-09138-5
- *The Astonishing Hypothesis: The Scientific Search For The Soul* (Scribner reprint edition, 1995) ISBN 0-684-80158-2
- Kreiseliana: about and around Georg Kreisel; ISBN 1-56881-061-X; 495 pages. For pages 25 − 32 "Georg Kreisel: a Few Personal Recollections" contributed by Francis Crick.

Books about Francis Crick and the structure of DNA discovery

- John Bankston, Francis Crick and James D. Watson; *Francis Crick and James Watson: Pioneers in DNA Research* (Mitchell Lane Publishers, Inc., 2002) ISBN 1-58415-122-6
- Soraya De Chadarevian; *Designs For Life: Molecular Biology After World War II*, CUP 2002, 444 pp; ISBN 0-521-57078-6
- Edwin Chargaff; *Heraclitean Fire*, Rockefeller Press, 1978
- S. Chomet (Ed.), "*D.N.A. Genesis of a Discovery*", 1994, Newman- Hemisphere Press, London
- Dickerson, Richard E.; "*Present at the Flood: How Structural Molecular Biology Came About*", Sinauer, 2005; ISBN 0-878-93168-6;
- Edward Edelson, "*Francis Crick And James Watson: And the Building Blocks of Life*"' Oxford University Press, 2000, ISBN 0-19-513971-2.

- John Finch; 'A Nobel Fellow On Every Floor', Medical Research Council 2008, 381 pp, ISBN 978-1840469-40-0; this book is all about the MRC Laboratory of Molecular Biology, Cambridge.
- Hager, Thomas; "*Force of Nature: The Life of Linus Pauling*", Simon & Schuster 1995; ISBN 0-684-80909-5
- Graeme Hunter; *Light Is A Messenger, the life and science of William Lawrence Bragg*, ISBN 0-19-852921-X; Oxford University Press, 2004.
- Horace Freeland Judson, *"The Eighth Day of Creation. Makers of the Revolution in Biology*"; Penguin Books 1995, first published by Jonathan Cape, 1977; ISBN 0-14-017800-7.
- Torsten Krude (Ed.); *DNA Changing Science and Society* (ISBN 0-521-82378-1) CUP 2003. (The Darwin Lectures for 2003, including one by Sir Aaron Klug on Rosalind Franklin's involvement in the determination of the structure of DNA).
- Brenda Maddox *Rosalind Franklin: The Dark Lady of DNA*, 2002. ISBN 0-00-655211-0.
- Robert Olby; *The Path to The Double Helix: Discovery of DNA*; first published in October 1974 by MacMillan, with foreword by Francis Crick; ISBN 0-486-68117-3; revised in 1994, with a 9-page postscript.
- Robert Olby; Oxford National Dictionary article: 'Crick, Francis Harry Compton (1916–2004)', Oxford Dictionary of National Biography, Oxford University Press, January 2008;
- Robert Olby; "Francis Crick: Hunter of Life's Secrets", Cold Spring Harbor Laboratory Press, ISBN 978-087969798-3, published on 25 August 2009. [73]
- Matt Ridley; *Francis Crick: Discoverer of the Genetic Code (Eminent Lives)* first published in June 2006 in the USA and then in the UK September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X.
- Anne Sayre. 1975. *Rosalind Franklin and DNA*. New York: W.W. Norton and Company. ISBN 0-393-32044-8.
- James D. Watson; *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, Atheneum, 1980, ISBN 0-689-70602-2 (first published in 1968) is a very readable firsthand account of the research by Crick and Watson. The book also formed the basis of the award winning television dramatization *Life Story* by BBC Horizon (also broadcast as *Race for the Double Helix*).
- James D. Watson; *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*; The Norton Critical Edition, which was published in 1980, edited by Gunther S. Stent: ISBN 0-393-01245-X. (It does not include Erwin Chargaff's critical review unfortunately.)
- James D. Watson; "Avoid boring people and other lessons from a life in science" New York: Random House. ISBN 978-0-375-41284-4, 366pp
- Maurice Wilkins; *The Third Man of the Double Helix: The Autobiography of Maurice Wilkins* ISBN 0-19-860665-6.

See also

- Neural correlates of consciousness
- Molecular structure of Nucleic Acids
- Crick's wobble hypothesis
- Crick, Brenner et al. experiment
- Reverse learning

External links

Crick papers

- [74] Crick's personal papers at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- Francis Crick Archive - Papers by Francis Crick are available for study at the Wellcome Library's Archives and Manuscripts department. These papers include those dealing with Crick's career after he moved to the Salk Institute in San Diego. The Crick papers [75]
- Comprehensive list of pdf files of Crick's papers from 1950 to 1990 [76] - National Library of Medicine.
- Francis Crick papers [77] - *Nature.com*
- http://www.intuition.org/txt/crick2.htm for Crick's comments on LSD
- Manuscripts and Correspondence - Mark Bretscher [78] Discovery of Crick's original scientific material in Cambridge, England.
- Key Participants: Francis H. C. Crick [79] - *Linus Pauling and the Race for DNA: A Documentary History*

Hear or see Crick

- An interview with Francis Crick and Christof Koch, 2001 [80]
- Listen to Francis Crick [81]
- Presentation speech [82] at the Nobel Prize ceremony in 1962.
- [83] web of stories video
- *The Quest for Consciousness* [84] - *The Quest for Consciousness* - 65 minute audio program - a conversation on Consciousness with neurobiologist Francis Crick of the Salk Institute and neurobiologist Christof Koch from Caltech.
- Listen [85] to Francis Crick and James Watson talking on the BBC in 1962, 1972, and 1974.
- The Impact of Linus Pauling on Molecular Biology [86] - a 1995 talk delivered by Crick at Oregon State University

About his work

- [75] The Crick Papers at the Wellcome Trust.
- "Quiet debut for the double helix" [87] by Professor Robert Olby, *Nature* **421** (23 January 2003): 402-405.
- Reading list [88] for discovery of DNA story from the National Centre for Biotechnology Education.

About his life

- Salk Institute Press Release [89] on the death of Francis Crick.
- BBC News: Francis Crick dies aged 88 [90]
- Francis Crick [91] (Archived [92] 2009-10-31) - MSN Encarta

Miscellaneous

- National DNA Day, 25 April 2006 Moderated Chat Transcript Archive [93]
- Obituary [94] in "The Times" (London) of Francis Crick, 30 July 2004.
- Independent On Line article [95] about Consciousness, 7 June 2006.
- Francis Crick Obituary [96] *The Biochemist*
- Obituary: Francis H. C. Crick (1916-2004) [97] by David M. Eagleman, in *Vision Research*
- Obituary: Francis Crick's Legacy for Neuroscience [98] by Ralph M. Siegel and Edward M. Callaway, in *PLoS Biology*
- 100 Scientists and Thinkers: James Watson and Francis Crick [99] from TIME magazine.
- Francis Crick: Nobel Prize 1962, Physiology or Medicine [100]
- Associated Press story on the death of Francis Crick [101]
- First press stories on DNA [13] but for the 'second' DNA story in *The New York Times*, see: http://www.nytimes.com/packages/pdf/science/dna-article.pdf - for reproduction of the original text in June 1953.
- 'Death' of DNA Helix (Crystalline) joke funeral card.
- Lynne Elkins' article on Franklin [102].
- 50th anniversary series of articles [103] -from *The New York Times*.
- Quotes [104] of Robert Olby on exactly who *may* have discovered the structure of DNA.
- listen to Matt Ridley [105] talking about Francis Crick.
- [106] A celebration of Francis Crick's life in science.
- The People's Archive interview [107]
- [108] Odile Crick's page (with music!) on the Crick family web site.
- [109] Obituary by Peter Lawrence and Mark Bretscher, "Current Biology".
- [110] Article by Mark Steyn from The Atlantic in 2004.
- [111] Review of "Francis Crick: Hunter of Life's Secrets" in 'Current Biology'.

References

[1] The Nobel Prize in Physiology or Medicine 1962 (http://nobelprize.org/medicine/laureates/1962/index.html). Nobel Prize Site for Nobel Prize in Physiology or Medicine 1962.

[2] Ridley, Matt (2006). *Francis Crick: discoverer of the genetic code*. [Ashland, OH: Atlas Books. pp. 192. ISBN 0-06-082333-X.

[3] Shermer, Michael (2004-07-30). "Astonishing Mind: Francis Crick 1916–2004" (http://www.skeptic.com/eskeptic/04-07-30.html). Skeptics Society. . Retrieved 2006-08-25.

[4] *A Nobel Fellow on Every Floor* John Finch - Darwin cited this corresponence in his last paper "On the dispersal of freshwater bivalves" *Nature* **25** 529-530

[5] Crick, Francis (1990). *What Mad Pursuit: a Personal View of Scientific Discovery*. Basic Books reprint edition. pp. 145. ISBN 0-465-09138-5. — Crick described himself as **agnostic, with a "strong inclination towards atheism"**.

[6] Chapters 1 and 2 of *What Mad Pursuit* by Francis Crick — provide Crick's description of his early life and education

[7] Page 13 of *What Mad Pursuit* by Francis Crick.

[8] *Nature*, Obituary, volume 430, 19 August 2004, p 845

[9] Bio at Wellcome Trust (http://genome.wellcome.ac.uk/doc_wtd021051.html)

[10] "Francis Crick, Co-Discoverer of DNA, Dies at 88" (http://query.nytimes.com/gst/fullpage.html?sec=health&res=9E06E7D7113DF933A05754C0A9629C8B63). *The New York Times*. 30 July 2004. . Retrieved 2007-07-21. "Francis H. C. Crick, co-discoverer of the structure of DNA, the genetic blueprint for life, and the leading molecular biologist of his age, died on Wednesday night in a hospital in San Diego. He was 88. He died after a long battle with colon cancer, said Andrew Porterfield, a spokesman for the Salk Institute, where he worked."

[11] Page 17 of *What Mad Pursuit* by Francis Crick.

[12] Page 18 of *What Mad Pursuit* by Francis Crick.

[13] Page 22 of *What Mad Pursuit* by Francis Crick.

[14] Page 30 of *The Eighth Day of Creation: Makers of the Revolution in Biology* by Horace Freeland Judson published by Cold Spring Harbor Laboratory Press (1996) ISBN 0-87969-478-5.

[15] Page 25 of *What Mad Pursuit* by Francis Crick.

[16] Page 32 of *What Mad Pursuit* by Francis Crick.

[17] Pages 33–34 of *What Mad Pursuit* by Francis Crick.

[18] Chapter 4 of *What Mad Pursuit* by Francis Crick.

[19] Page 46 of *What Mad Pursuit* by Francis Crick. "..there was no alternative but to teach X-ray diffraction to myself."

[20] Atomic Coordinates and Structure Factors for Two Helical Configurations of Polypeptide Chains (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=14834145) by Linus Pauling and Robert B. Corey in Proc Natl Acad Sci U S A (1951) volume 37, pages 235−240.

[21] Page 58 of *What Mad Pursuit* by Francis Crick.

[22] Cochran W, Crick FHC and Vand V. (1952) "The Structure of Synthetic Polypeptides. I. The Transform of Atoms on a Helix", *Acta Cryst.*, **5**, 581-586.

[23] See "*Evidence for the Pauling-Corey alpha-Helix in Synthetic Polypeptides*" (1952) *Nature* Volume 169 pages 234−235 (download PDF (http://profiles.nlm.nih.gov/SC/B/C/D/M/_/scbcdm.pdf)). Crick's scientific publications and letters are in the list of Francis Crick's Papers (http://profiles.nlm.nih.gov/SC/) from the Wellcome Library or the National Library of Medicine.

[24] Molecular structure of Nucleic Acids (http://profiles.nlm.nih.gov/SC/B/B/Y/W/_/scbbyw.pdf) by James D. Watson and Francis H. C. Crick. *Nature* **171**, 737−738 (1953).

[25] Francis Crick's 1962 Biography from the Nobel foundation (http://nobelprize.org/medicine/laureates/1962/crick-bio.html).

[26] Crick traced his interest in the physical nature of the gene back to the start of his work in biology, when he was in the Strangeways laboratory; Page 22 of *What Mad Pursuit* by Francis Crick.

[27] In *The Eighth Day of Creation*, Horace Judson describes the development of Watson's thinking about the physical nature of genes. On page 89, Judson explains that by the time Watson came to Cambridge, he believed genes were made of DNA and he hoped that he could use X-ray diffraction data to determine the structure.

[28] Page 90, In *The Eighth Day of Creation* by Horace Judson.

[29] Linus Pauling and the Race for DNA: A Documentary History (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/narrative/page13.html) Special Collections, The Valley Library, Oregon State University.

[30] Chapter 3 in *The Eighth Day of Creation* by Horace Judson.

[31] M. F. Perutz, J. T. Randall, L. Thomson, M. H. Wilkins J. D. Watson (June 1969). "DNA helix". *Science* **27**: 1537−1539. doi: 10.1126/science.164.3887.1537 (http://dx.doi.org/10.1126/science.164.3887.1537). PMID 5796048 (http://www.ncbi.nlm.nih.gov/pubmed/5796048).

[32] Franklin's citation to the earlier work of W. T. Astbury is in:
Franklin RE, Gosling RG (April 1953). "Molecular configuration in sodium thymonucleate" (http://www.nature.com/nature/dna50/franklingosling.pdf) (PDF reprint). *Nature* **171** (4356): 740−1. doi: 10.1038/171740a0 (http://dx.doi.org/10.1038/171740a0). PMID 13054694 (http://www.ncbi.nlm.nih.gov/pubmed/13054694). .

[33] Crick F (April 1974). "The double helix: a personal view". Nature **248** (5451): 766−9. doi: 10.1038/248766a0 (http://dx.doi.org/10.1038/248766a0). PMID 4599081 (http://www.ncbi.nlm.nih.gov/pubmed/4599081).

[34] In chapter 3 of *The Eighth Day of Creation*, Horace Judson describes the development of Watson's and Crick's thinking about the structure of DNA and how it evolved during their model building. Watson and Crick were open to the idea of tentatively ignoring all individual experimental results, in case they might be wrong or misleading. Judson describes how Watson spent a large amount of time *ignoring* Crick's belief (based on Franklin's determination of the space group) that the two backbone strands were antiparallel. On page 176, Judson quotes a letter written by Watson, "The model has been derived almost entirely from stereochemical considerations with the only X-ray consideration being the spacing between the pair of bases 3.4 A which was originally found by Astbury."

[35] See Chapter 3 of *The Eighth Day of Creation: Makers of the Revolution in Biology* by Horace Freeland Judson published by Cold Spring Harbor Laboratory Press (1996) ISBN 0-87969-478-5. Judson also lists the publications of W. T. Astbury that described his early X-ray diffraction results for DNA.

[36] Page 75 of *What Mad Pursuit* by Francis Crick. "If Jim had been killed by a tennis ball, I am reasonably sure I would not have solved the structure alone".

[37] http://www.farooqhussain.org/projects/

[38] Watson JD, Crick FH (May 1953). "Genetical implications of the structure of deoxyribonucleic acid" (http://profiles.nlm.nih.gov/SC/B/B/Y/X/_/scbbyx.pdf) (PDF reprint). *Nature* **171** (4361): 964−7. doi: 10.1038/171964b0 (http://dx.doi.org/10.1038/171964b0). PMID 13063483 (http://www.ncbi.nlm.nih.gov/pubmed/13063483). .

[39] *Morgan, G.J. (2003). "Historical Review: Viruses, Crystals and Geodesic Domes". *Trends in Biochemical Sciences* **28**: 86−90. doi: 10.1016/S0968-0004(02)00007-5 (http://dx.doi.org/10.1016/S0968-0004(02)00007-5)..

[40] Rich A, Crick FH (November 1955). "The structure of collagen" (http://profiles.nlm.nih.gov/SC/B/B/Z/L/_/scbbzl.pdf) (PDF reprint). *Nature* **176** (4489): 915−6. doi: 10.1038/176915a0 (http://dx.doi.org/10.1038/176915a0). PMID 13272717 (http://www.ncbi.nlm.nih.gov/pubmed/13272717). .

[41] " On Degenerate Templates and the Adaptor Hypothesis: A Note for the RNA Tie Club (http://profiles.nlm.nih.gov/SC/B/B/G/F/_/scbbgf.pdf)" by Francis Crick (1956).

[42] Crick FH (1958). "On protein synthesis" (http://profiles.nlm.nih.gov/SC/B/B/Z/Y/_/scbbzy.pdf) (PDF reprint). *Symp. Soc. Exp. Biol.* **12**: 138−63. PMID 13580867 (http://www.ncbi.nlm.nih.gov/pubmed/13580867). .

[43] Crick FH, Barnett L, Brenner S, Watts-Tobin RJ (December 1961). "General nature of the genetic code for proteins" (http://profiles.nlm.nih.gov/SC/B/C/B/J/_/scbcbj.pdf) (PDF reprint). *Nature* **192**: 1227−32. doi: 10.1038/1921227a0 (http://dx.doi.org/10.1038/1921227a0). PMID 13882203 (http://www.ncbi.nlm.nih.gov/pubmed/13882203). .

[44] Crick FH (April 1967). "The Croonian lecture, 1966. The genetic code" (http://profiles.nlm.nih.gov/SC/B/C/B/X/_/scbcbx.pdf) (PDF reprint). *Proc. R. Soc. Lond., B, Biol. Sci.* **167** (9): 331–47. doi: 10.1098/rspb.1967.0031 (http://dx.doi.org/10.1098/rspb.1967.0031). PMID 4382798 (http://www.ncbi.nlm.nih.gov/pubmed/4382798). .

[45] Chapter 3 of *The Eighth Day of Creation: Makers of the Revolution in Biology* by Horace Freeland Judson published by Cold Spring Harbor Laboratory Press (1996) ISBN 0-87969-478-5.

[46] *Maurice Wilkins; The Third Man of the Double Helix* by Maurice Wilkins (ISBN 0-19-860665-6). Wilkins provides a detailed account of the fact that Franklin's results were interpreted as most likely indicated three, and possibly four, polynucleotide strands in the DNA molecule.

[47] *Rosalind Franklin: The Dark Lady of DNA* by Brenda Maddox. (2002) ISBN 0-06-018407-8.

[48] McKie, Robin (2006-09-17). "Genius was in his DNA" (http://books.guardian.co.uk/reviews/biography/0,,1874072,00.html). *The Guardian*. . Retrieved 2007-08-04.

[49] *Of Molecules and Men* (Prometheus Books, 2004; original edition 1967) ISBN 1-59102-185-5. A portion of the book was published as " The Computer, the Eye, the Soul (http://profiles.nlm.nih.gov/SC/B/C/F/F/_/scbcff.pdf)" in *Saturday Review* (1966): 53–55.

[50] Francis Crick refers to himself as a sceptic and an agnostic with "a strong inclination towards atheism", see reference 42.

[51] Beckett C (April 2004). "For the record: the Francis Crick Archive at the Wellcome Library" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=546341). *Med Hist* **48** (2): 245–60. PMID 15151106 (http://www.ncbi.nlm.nih.gov/pubmed/15151106).
See also e.g. Telegraph Article (http://www.telegraph.co.uk/connected/main.jhtml?xml=/connected/2003/03/19/ecfgod19.xml)

[52] Crick F (November 1970). "Molecular biology in the year 2000" (http://profiles.nlm.nih.gov/SC/B/C/C/J/_/scbccj.pdf) (PDF reprint). *Nature* **228** (5272): 613–5. doi: 10.1038/228613a0 (http://dx.doi.org/10.1038/228613a0). PMID 4920018 (http://www.ncbi.nlm.nih.gov/pubmed/4920018). .

[53] Borg J, Andrée B, Soderstrom H, Farde L (November 2003). "The serotonin system and spiritual experiences" (http://ajp.psychiatryonline.org/cgi/pmidlookup?view=long&pmid=14594742). *Am J Psychiatry* **160** (11): 1965–9. doi: 10.1176/appi.ajp.160.11.1965 (http://dx.doi.org/10.1176/appi.ajp.160.11.1965). PMID 14594742 (http://www.ncbi.nlm.nih.gov/pubmed/14594742). .

[54] Crick FH (December 1968). "The origin of the genetic code" (http://linkinghub.elsevier.com/retrieve/pii/0022-2836(68)90392-6). *J. Mol. Biol.* **38** (3): 367–79. doi: 10.1016/0022-2836(68)90392-6 (http://dx.doi.org/10.1016/0022-2836(68)90392-6). PMID 4887876 (http://www.ncbi.nlm.nih.gov/pubmed/4887876). .

[55] " Directed Panspermia (http://profiles.nlm.nih.gov/SC/B/C/C/P/_/scbccp.pdf)" by Francis Crick and Leslie E Orgel in *Icarus* (1973) Volume 19 pages 341–346. Crick later wrote a book about directed panspermia: Crick, Francis (1981). *Life itself: its origin and nature*. New York: Simon and Schuster. ISBN 0-671-25562-2.

[56] Orgel LE, Crick FH (January 1993). "Anticipating an RNA world. Some past speculations on the origin of life: where are they today?" (http://www.fasebj.org/cgi/reprint/7/1/238.pdf) (PDF reprint). *Faseb J.* **7** (1): 238–9. PMID 7678564 (http://www.ncbi.nlm.nih.gov/pubmed/7678564). .

[57] F.H.C. Crick, S. Brenner and A. Klug, *A speculation on the origin of protein synthesis,* Origins of Life (journal), 7:389-397 (1976)

[58] http://www.gen.cam.ac.uk/About/News/departmenthistory.htm

[59] Page 145 of *What Mad Pursuit* by Francis Crick.

[60] " Towards a Neurobiological Theory of Consciousness (http://profiles.nlm.nih.gov/SC/B/C/F/D/_/scbcfd.pdf)" by Francis Crick and Christof Koch in *Seminars in the Neurosciences* (1990): Volume 2 pages 263–275.

[61] *The Astonishing Hypothesis: The Scientific Search For The Soul* by Francis Crick. (Scribner reprint edition, 1995) ISBN 0-684-80158-2

[62] Watson's book *The Double Helix* painted a vivid image of Crick, starting with the famous line, "I have never seen Francis Crick in a modest mood." The first chapter of Horace Judson's book *The Eighth Day of Creation* describes the importance of Crick's talking and his boldness in his scientific style.

[63] Describing Crick's influence on his scientific colleagues, Francis Crick Papers archivist Chris Beckett wrote of the importance of, ".....Crick's presence and eloquence —direct and beguiling, by all accounts in the archive— at conference after conference, through formal lectures, extempore summaries, informal meetings and individual conversations. Indeed, one has the impression that it was through these frequent persuasive moments of personal delivery and purposive conversations that Crick was most influential."
Beckett C (April 2004). "For the record: the Francis Crick Archive at the Wellcome Library" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=546341). *Med Hist* **48** (2): 245–60. PMID 15151106 (http://www.ncbi.nlm.nih.gov/pubmed/15151106).. Also described as an example of Crick's wide recognition and public profile are some of the times Crick was addressed as "Sir Francis Crick" with the assumption that someone so famous must have been knighted.

[64] Eagleman, D.M. (2005). Obituary: Francis H. C. Crick (1916-2004). (http://neuro.bcm.edu/eagleman/papers/Eagleman_Crick_VisionResearch2005.pdf) Vision Research. 45: 391-393.

[65] *Francis Crick: Discoverer of the Genetic Code* by Matt Ridley, published in 2006 by HarperCollins Publishers.

[66] Intelligent design tied to creationism in Dover trial (http://www.post-gazette.com/pg/05271/578955.stm) by Bill Toland for the *Pittsburgh Post-Gazette* (28 September 2005).

[67] Amicus Curiae Brief of 72 Nobel Laureates, 17 State Academies of Science, and 7 Other Scientific Organization in Support of Appellees (http://www.talkorigins.org/faqs/edwards-v-aguillard/amicus1.html) filed in the case *Edwards v. Aguillard* before the U.S. Supreme Court (1986).

[68] Press release from the British Humanist Association: Darwin Day a natural holiday? (http://www.humanism.org.uk/site/cms/contentViewArticle.asp?article=1348) (12 February 2003).

[69] The Francis Crick Lecture (2003) (http://www.royalsoc.ac.uk/page.asp?tip=1&id=1809): **The Royal Society** website. Retrieved 12 July 2006

[70] *Back and Forward: From University to Research Institute; From Egg to Adult, and Back Again* (http://www.bio.cam.ac.uk/gradschool/ adverts/johngurdon.html) by Professor Sir John Gurdon, Francis Crick Graduate Lectures, 29 November 2005. **University of Cambridge**. Retrieved 12 July 2006.

[71] *A Life in Science* (http://www.bio.cam.ac.uk/gradschool/adverts/timhunt-review.html) by Dr Tim Hunt, Francis Crick Graduate Lectures, 29 June 2005. **University of Cambridge**. Retrieved 12 July 2006.

[72] http://www.westminster.gov.uk/councilgovernmentanddemocracy/councils/pressoffice/news/pr-3802.cfm

[73] http://www.cshlpress.com/pdf/sample/Crick.pdf

[74] http://orpheus.ucsd.edu/speccoll/testing/html/mss0660a.html#abstract

[75] http://genome.wellcome.ac.uk/node30074.html

[76] http://profiles.nlm.nih.gov/SC/Views/AlphaChron/date/10002/

[77] http://www.nature.com/nature/focus/crick/index.html

[78] http://www2.mrc-lmb.cam.ac.uk/archive/manu-corr-bretscher.html

[79] http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/people/crick.html

[80] http://www.artboy.info/strange/listen.html

[81] http://www.bl.uk/onlinegallery/features/beautifulminds/sounds.html#compton

[82] http://nobelprize.org/medicine/laureates/1962/press.html

[83] http://www.webofstories.com/person.html?cat=3&pers=1018&st=13844

[84] http://www.artboy.info/strange/listen.html#Christof1

[85] http://www.bbc.co.uk/bbcfour/audiointerviews/profilepages/crickwatson1.shtml

[86] http://osulibrary.oregonstate.edu/specialcollections/events/1995paulingconference/video-s1-2-crick.html

[87] http://chem-faculty.ucsd.edu/joseph/CHEM13/DNA1.pdf

[88] http://www.ncbe.reading.ac.uk/DNA50/reviews.html

[89] http://www.salk.edu/news/releases/details.php?id=103

[90] http://news.bbc.co.uk/2/hi/science/nature/3937475.stm

[91] http://encarta.msn.com/encyclopedia_761568380/Francis_Crick.html

[92] http://www.webcitation.org/5kwcLocoT

[93] http://www.genome.gov/18516768

[94] http://www.timesonline.co.uk/tol/news/uk/health/article463763.ece

[95] http://news.independent.co.uk/world/science_technology/article702961.ece

[96] http://www.biochemist.org/bio/02605/0080/026050080.pdf

[97] http://neuro.bcm.edu/eagleman/papers/Eagleman_Crick_VisionResearch2005.pdf

[98] http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pbio.0020419

[99] http://www.time.com/time/time100/scientist/profile/watsoncrick.html

[100] http://www2.mrc-lmb.cam.ac.uk/archive/Crick62.html

[101] http://www.msnbc.msn.com/id/5549247

[102] http://www.physicstoday.org/vol-56/iss-3/p42.html

[103] http://www.nytimes.com/indexes/2003/02/25/health/genetics/index.html

[104] http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/quotes/olby.html

[105] http://www.eyeonbooks.com/ibp.php?ISBN=006082333X

[106] http://www.packer34.freeserve.co.uk/rememberingfranciscrickacelebration.htm

[107] http://peoplesarchive.com/browse/movies/4941/

[108] http://www.crick.com/odile.html

[109] http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VRT-4D56PX0-6&_user=10&_rdoc=1&_fmt=&_orig=search& _sort=d&view=c&_version=1&_urlVersion=0&_userid=10&md5=933cd68a0e3485f54920d0cbb35a428a

[110] http://www.theatlantic.com/doc/200410/steyn

[111] http://www.mrc-lmb.cam.ac.uk/PAL/NewFiles/PAListFrames.html

Maurice Wilkins

Maurice Wilkins	
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Born	15 December 1916 Pongaroa, Wairarapa, New Zealand
Died	5 October 2004 (aged 87) Blackheath, London, United Kingdom
Nationality	New Zealand
Fields	molecular biologist,
Known for	X-ray diffraction, DNA
Notable awards	Nobel Prize in Physiology or Medicine (1962)

Maurice Hugh Frederick Wilkins CBE FRS (15 December 1916 – 5 October 2004) was a New Zealand molecular biologist, and Nobel Laureate who contributed research in the fields of phosphorescence, radar, isotope separation, and X-ray diffraction. He was most widely known for his work at King's College London on the structure of DNA. In recognition of this work, he, Francis Crick and James Watson were awarded the 1962 Nobel Prize for Physiology or Medicine, "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material."[1]

Birth and education

Monument to Maurice Wilkins, Main Street, Pongaroa, New Zealand

Wilkins was born in Pongaroa, north Wairarapa, New Zealand where his father, Edgar Henry Wilkins was a medical doctor. His family moved to Birmingham, England when he was 6, where he subsequently attended Wylde Green College and then King Edward's School at the age of 12. He later studied physics at St John's College, Cambridge, then in 1940 he received his Ph.D. in physics at the University of Birmingham with a dissertation on phosphors. During World War II he developed improved radar screens at Birmingham, then worked on isotope separation at the Manhattan Project at the University of California, Berkeley for two years before returning to King's College London. "After the war I wondered what I would do, as I was very disgusted with the dropping of two bombs on civilian centres in Japan," he told Britain's Encounter radio programme in 1999.[2]

Academic career

In 1946 the physicist John Randall was placed in charge of a new biophysics laboratory at King's College. The plan was to hire physicists such as Wilkins to work on problems in biology. When Francis Crick first met Wilkins he was not convinced that the King's College laboratory had anything like a clear plan of attack. There seemed to be a vague hope that by applying techniques like Ultraviolet light microscopy (Wilkins) and electron microscopy (Randall), new insights could be gained into cell structure and function. By 1950, Randall was gearing up the laboratory for work on proteins. His original plan for Rosalind Franklin was that she do X-ray diffraction studies on proteins. Wilkins' work on DNA changed that. By 1951, Randall had established a major effort to solve the structure of collagen and Wilkins and Franklin represented a parallel effort to determine the structure of DNA. In the meantime, Maurice Wilkins' friend Francis Crick had joined forces with James Watson under the supervision of Max Perutz at the Cavendish Laboratory, Cambridge and under the overall direction of Lawrence Bragg.

DNA

At King's College Wilkins pursued, among other things x-ray diffraction work on DNA that had been obtained from calf thymus by the Swiss scientist Rudolf Signer. The DNA from Signer's lab was much more intact than the DNA which had previously been isolated. Wilkins discovered that it was possible to produce thin threads from this concentrated DNA solution that contained highly ordered arrays of DNA suitable for the production of x-ray diffraction patterns.[3] Using a carefully bundled group of these DNA threads and keeping them hydrated, Wilkins and a graduate student Raymond Gosling obtained x-ray photographs of DNA that showed that the long, thin DNA molecule in the sample from Signer had a regular, crystal-like structure in these threads. This initial x-ray diffraction work at Kings College was done in May or June 1950. It was one of the x-ray diffraction photographs taken in 1950, shown at a meeting in Naples a year later, that sparked James Watson's interest in DNA.

At that time Wilkins also introduced Francis Crick to the importance of DNA. Wilkins knew that proper experiments on the threads of purified DNA would require better x-ray equipment. Wilkins ordered a new x-ray tube and a new microcamera. Before the DNA sample from Signer was available, Gosling had been trying to make x-ray diffraction images of sperm. However, Franklin did not start using the new equipment until September 1951. By the summer of 1950 Randall had arranged for a three year research fellowship that would fund Rosalind Franklin in his laboratory. Franklin was delayed in finishing her work in Paris. Late in 1950, Randall wrote to Franklin to inform her that rather than work on protein, she should take advantage of Wilkins's preliminary work and that she should do x-ray studies of DNA fibers made from Signer's samples of DNA. Early in 1951 Franklin finally arrived. Wilkins was away on holiday and missed an initial meeting at which Raymond Gosling stood in for him along with Alex Stokes, who, like Crick, would solve the basic mathematics that make possible a general theory of how helical structures diffract x-rays. No work had been done on DNA in the laboratory for several months; the new x-ray tube sat unused, waiting for Franklin. Franklin ended up with the DNA from Signer, Gosling became her PhD student, and she had the expectation that DNA x-ray diffraction work was her project. Wilkins returned to the laboratory expecting that Franklin would be his collaborator and that they would work together on the DNA project that he had started. Franklin felt that DNA was now her project and would not collaborate with Wilkins, who then pursued parallel studies.

By November 1951 Wilkins had evidence that DNA in cells as well as purified DNA had a helical structure.[4] Alex Stokes had solved the basic mathematics of helical diffraction theory and thought that Wilkins's x-ray diffraction data indicated a helical structure in DNA. Wilkins met with Watson and Crick and told them about his results. This information from Wilkins, along with additional information gained by Watson when he heard Franklin talk about her research during a King's College research meeting, stimulated Watson and Crick to create their first molecular model of DNA, a model with the phosphate backbones at the center. Upon viewing the model of the proposed structure, Franklin told Watson and Crick that it was wrong. Franklin knew from basic chemical principles the hydrophilic backbones should go on the outside of the molecule where they could interact with water. Crick tried to

get Wilkins to continue with additional molecular modeling efforts, but Wilkins did not take this approach. During 1952, Franklin also refused to participate in molecular modeling efforts and continued to work on step-by-step detailed analysis of her x-ray diffraction data (Patterson synthesis). By the spring of 1952, Franklin had received permission from Randall to ask to transfer her fellowship so that she could leave King's College and work in John Bernal's laboratory at Birkbeck College, also in London. However, Franklin remained at King's College for another year.

By early 1953, it was clear that Franklin would simply drop her DNA work at the end of her fellowship that summer, or even sooner due to illness. Linus Pauling had published a proposed but incorrect structure of DNA, making the same basic error that Watson and Crick had made a year earlier. Some of those working on DNA in the United Kingdom feared that Pauling would quickly solve the DNA structure once he recognized his error and put the backbones of the nucleotide chains on the outside of a model of DNA. After March 1952 Franklin concentrated on the x-ray data for the A-form of less hydrated DNA while Wilkins tried to work on the hydrated B-form. Wilkins was handicapped because Franklin had all of the good DNA. Wilkins got new DNA samples, but it was not as good as the original sample he had used in 1950 and which Franklin continued to use. Most of his new results were for biological samples like sperm cells, which seemed to also suggest a helical structure for DNA. In the middle of 1952 Wilkins had for a time abandoned further DNA work when Franklin reported to him that her results made her doubt the helical nature of the A-form. Wilkins feared that the data suggesting a helical structure might just be an artifact.

In early 1953 Watson visited King's College and Wilkins showed him a high quality image of the B-form x-ray diffraction pattern, now nicknamed photo 51, that Franklin had produced in March 1952. With the knowledge that Pauling was working on DNA and had submitted a model of DNA for publication, Watson and Crick mounted one more concentrated effort to deduce the structure of DNA. Through from Max Perutz, his thesis supervisor, Crick gained access to a progress report from King's College that included useful information from Franklin about the features of DNA she had deduced from her x-ray diffraction data. Watson and Crick published their proposed DNA double helical structure in a paper in the journal *Nature* in April 1953. In this paper Watson and Crick acknowledged that they had been "stimulated by.... the unpublished results and ideas" of Wilkins and Franklin.

The discovery itself was made on 28 February 1953 by Watson and Crick; the first Watson-Crick paper appeared in Nature on 25 April 1953. Sir Lawrence Bragg, the director of the Cavendish Laboratory, where Watson and Crick worked, gave a talk at Guys Hospital Medical School in London on Thursday 14 May 1953 which resulted in an article by Ritchie Calder in The News Chronicle of London, on Friday 15 May 1953, entitled "Why You Are You. Nearer Secret of Life." The news reached readers of The New York Times the next day; Victor K. McElheny, in researching his biography of Watson, "Watson and DNA: Making a Scientific Revolution", found a clipping of a six-paragraph *New York Times* article written from London and dated 16 May 1953 with the headline "Form of 'Life Unit' in Cell Is Scanned." The article ran in an early edition and was then pulled to make space for news deemed more important. (The *New York Times* subsequently ran a longer article on 12 June 1953). The Cambridge University undergraduate newspaper *Varsity* also ran its own short article on the discovery on Saturday 30 May 1953. Bragg's original announcement at a Solvay conference on proteins in Belgium on 8 April 1953 went unreported by the press.

In recognition of the contribution from King's College, Watson and Crick agreed that Wilkins, Stokes, and Wilson[5] and Franklin and Gosling should each publish their x-ray diffraction work, which supported the proposed Crick-Watson model, in separate articles in the same issue of *Nature*.

Wilkins and others went on to repeat and extend much of Franklin's work, and produced abundant evidence to support the helical model produced by Crick and Watson.

Wilkins married his second wife Patricia Ann Chidgey in 1959. They had four children, Sarah, George, Emily and William; he had a son by his previous marriage, to an art student called Ruth in California.

He published his autobiography, "The Third Man of the Double Helix," in 2003, but does not specifically credit Stokes and Wilson as co-authors of their paper in "Nature". Whether this was deliberate on his part or just the result

of poor sub-editing by the publisher is not known.

Recognition

In 1960 he was presented with the American Public Health Association's Albert Lasker Award, and in 1962 he was made a Commander of the British Empire. Also in 1962 he shared the Nobel Prize in Physiology or Medicine with Watson and Crick for the discovery of the structure of DNA.

On Saturday 20 October 1962 the award of Nobel prizes to John Kendrew and Max Perutz, and to Crick, Watson, and Wilkins was satirised in a short sketch in the BBC TV programme That Was The Week That Was with the Nobel Prizes being referred to as 'The Alfred Nobel Peace Pools.'

In 2000, King's College London opened the *Franklin-Wilkins Building* in honour of Dr. Franklin's and Professor Wilkins' work at the college.[6]

A plaque commemorating Maurice Wilkins and his discovery, beneath the monument, Pongaroa, New Zealand

The wording on the new DNA sculpture (which was donated by James Watson) outside Clare College's Thirkill Court, Cambridge, England is

a) on the base:

> i) "These strands unravel during cell reproduction. Genes are encoded in the sequence of bases."

> ii) "The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins."

b) on the helices:

> i) "The structure of DNA was discovered in 1953 by Francis Crick and James Watson while Watson lived here at Clare."

> ii) "The molecule of DNA has two helical strands that are linked by base pairs Adenine - Thymine or Guanine - Cytosine."

References

[1] The Nobel Prize in Physiology or Medicine 1962 (http://nobelprize.org/medicine/laureates/1962/index.html). Nobel Prize Site for Nobel Prize in Physiology or Medicine 1962.

[2] "A Bunch of Genes" (http://www.abc.net.au/rn/relig/enc/stories/s39549.htm). Radio National. 4 July 1999. . Retrieved 2009-02-20.

[3] See Figure 1 of the Nobel lecture by Wilkins (http://nobelprize.org/medicine/laureates/1962/wilkins-lecture.html). See other examples (http://www.kcl.ac.uk/depsta/iss/archives//dna/faq8-2.html) at the King's College website for DNA structure.

[4] See Chapter 2 of *The Eighth Day of Creation: Makers of the Revolution in Biology* by Horace Freeland Judson published by Cold Spring Harbor Laboratory Press (1996) ISBN 0-87969-478-5.

[5] "Molecular Structure of Deoxypentose Nucleic Acids" by M. H. F. Wilkins, A.R. Stokes A.R. and H. R. Wilson in *Nature* (1953) volume 171 pages 738-740. Download the full text (http://www.nature.com/nature/dna50/wilkins.pdf) in PDF format.

[6] Maddox, p. 323

1. Watson, James D. "The Double Helix: A Personal Account of the Discovery of the Structure of DNA"; The Norton Critical Edition, which was published in 1980, edited by Gunther S. Stent.

Books featuring Maurice Wilkins

- Robert Olby; 'Wilkins, Maurice Hugh Frederick (1916-2004), Oxford Dictionary of National Biography, online edn, Oxford University Press, Jan 2008
- Robert Olby; "Francis Crick: Hunter of Life's Secrets", Cold Spring Harbor Laboratory Press, ISBN 9780879697983, published in August 2009.
- John Finch; 'A Nobel Fellow On Every Floor', Medical Research Council 2008, 381 pp, ISBN 978-1840469-40-0; this book is all about the MRC Laboratory of Molecular Biology, Cambridge
- Robert Olby; "The Path to The Double Helix: Discovery of DNA"; first published in October 1974 by MacMillan, with foreword by Francis Crick; ISBN 0-486-68117-3; the definitive DNA textbook, revised in 1994, with a 9 page postscript.
- Horace Freeland Judson, "The Eighth Day of Creation. Makers of the Revolution in Biology"; CSHL Press 1996 ISBN 0-87969-478-5.
- Watson, James D. *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*; The Norton Critical Edition , which was published in 1980, edited by Gunther S. Stent:ISBN 0-393-01245-X.
- Chomet, S. (Ed.), *D.N.A. Genesis of a Discovery*, 1994, Newman- Hemisphere Press, London; NB a few copies are available from Newman-Hemisphere at 101 Swan Court, London SW3 5RY (phone: 07092 060530).
- Maddox, Brenda, Rosalind Franklin: The Dark Lady of DNA, 2002. ISBN 0-06-018407-8.
- Sayre, Anne 1975. Rosalind Franklin and DNA. New York: W.W. Norton and Company. ISBN 0-393-32044-8.
- Wilkins, Maurice, The Third Man of the Double Helix: The Autobiography of Maurice Wilkins ISBN 0-19-860665-6.
- Crick, Francis, 1990. What Mad Pursuit: A Personal View of Scientific Discovery (Basic Books reprint edition) ISBN 0-465-09138-5
- Watson, James D., The Double Helix: A Personal Account of the Discovery of the Structure of DNA, Atheneum, 1980, ISBN 0-689-70602-2 (first published in 1968)
- Krude, Torsten (Ed.) DNA Changing Science and Society: The Darwin Lectures for 2003 CUP 2003, includes a lecture by Sir Aaron Klug on Rosalind Franklin's involvement in the determination of the structure of DNA.
- Ridley, Matt; "Francis Crick: Discoverer of the Genetic Code (Eminent Lives)" was first published in June 2006 in the USA and then in the UK September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X; this short book is in the publisher's "Eminent Lives" series.
- "Light Is A Messenger, the life and science of William Lawrence Bragg" by Graeme Hunter, ISBN 0-19-852921-X; Oxford University Press, 2004.
- "Designs For Life: Molecular Biology After World War II" by Soraya De Chadarevian; CUP 2002, 444 pp; ISBN 0-521-57078-6; it includes James Watson's "well kept open secret" from April 2003!
- Tait, Sylvia & James "A Quartet of Unlikely Discoveries" (Athena Press 2004) ISBN 184401343X

External links

- (http://www.independent.co.uk/news/obituaries/professor-maurice-wilkins-543103.html) Obituary from The Independent on Sunday,9 October 2004.
- (http://orpheus.ucsd.edu/speccoll/testing/html/mss0660a.html#abstract) Crick's personal papers at Mandeville Special Collections Library,Geisel Library,University of California, San Diego
- "Quiet debut for the double helix" (http://chem-faculty.ucsd.edu/joseph/CHEM13/DNA1.pdf) by Professor Robert Olby, *Nature* **421** (January 23, 2003): 402-405.
- (http://www.peoplesarchive.com/) for the People's Archive/BBC 90 story interview with Crick AND the 236 story interview with Brenner.
- (http://nobelprize.org/medicine/laureates/1962/press.html) Presentation speech at the Nobel Prize ceremony in 1962.

- Reading University site on 50th anniversary of Discovery of the structure of DNA (http://www.ncbe.reading. ac.uk/DNA50/reviews.html). Includes a list of Books (http://www.ncbe.reading.ac.uk/DNA50/reviews. html) on the subject.
- Biography (from Nobel) (http://www.nobel.se/medicine/laureates/1962/wilkins-bio.html)
- Biography (from the New Zealand Edge) (http://www.nzedge.com/heroes/wilkins.html)
- Discovery Story in BA Magazine (http://www.ba-education.demon.co.uk/for/science/dnamain.html)
- DNA: The King's Story detailing Wilkins' involvement in elucidating the structure of DNA (http://www.kcl.ac. uk/depsta/iss/archives//dna/)
- List of classic papers in *Nature* on DNA structure (http://www.nature.com/nature/dna50/archive.html)
- Listen to Francis Crick and James Watson talking on the BBC (http://www.bbc.co.uk/bbcfour/ audiointerviews/profilepages/crickwatson1.shtml)
- (http://www.nytimes.com/packages/pdf/science/dna-article.pdf) - for reproduction of the original text in June 1953.
- (http://www.physicstoday.org/vol-56/iss-3/p42.html) for Lynne Elkins' article on Franklin.
- New York Times 50th anniversary series (http://www.nytimes.com/indexes/2003/02/25/health/genetics/ index.html) of excellent articles.
- (http://www.nytimes.com/packages/pdf/science/dna-article.pdf) The first American newspaper coverage of the discovery of the DNA structure: Saturday, June 13, 1953 The New York Times

Rosalind Franklin

Rosalind Franklin	
Rosalind Franklin	
Born	Notting Hill, London, United Kingdom
Died	(aged 37) Chelsea, London, United Kingdom Cancer of the ovary
Nationality	British
Fields	X-ray crystallography
Institutions	British Coal Utilisation Research Association *Laboratoire central des services chimiques de l'État* King's College London Birkbeck College, London
Alma mater	Newnham College, Cambridge
Known for	Fine structure of coal and graphite, DNA structure, viruses

Rosalind Elsie Franklin (25 July 1920 – 16 April 1958) was a British biophysicist, physicist, chemist, biologist and X-ray crystallographer who made important contributions to the understanding of the fine molecular structures of DNA, RNA, viruses, coal and graphite.

Franklin is still best known for her work on the X-ray diffraction images of DNA. Her data, according to Francis Crick, was "the data we actually used"[1] to formulate Crick and Watson's 1953 hypothesis regarding the structure of DNA.[2] Furthermore, unpublished drafts of her papers (written as she was arranging to leave the unsupportive research situation at King's College London) show that she had indeed determined the overall B-form of the DNA helix. However, her work was published third, in the series of three DNA *Nature* articles, led by the paper of Watson and Crick which only vaguely acknowledged her evidence in support of their hypothesis.[3] The possibility of Franklin having played a major role was not revealed until Watson wrote his personal account, *The Double Helix*,[4] in 1968 which subsequently inspired several people to investigate DNA history and Franklin's contribution. The first, Robert Olby's "The Path to the Double Helix", supplied information about original source materials for those that followed.[5] After finishing her portion of the DNA work, Franklin led pioneering work on the tobacco mosaic and polio viruses.

She died at the age of 37 from complications arising from ovarian cancer.

Background

Franklin was born in Notting Hill, London[6] into an affluent and influential British-Jewish family.[7] Her father was Ellis Arthur Franklin (1894–1964), a London merchant banker and her mother was Muriel Frances Waley (1894–1976); she was the elder daughter and second of the family of five children.

Her uncle was Herbert Samuel (later Viscount Samuel) who was Home Secretary in 1916 and the first practicing Jew to serve in the British Cabinet.[8] He was also the first High Commissioner (effectively governor) for the British Mandate of Palestine.

Her aunt Helen Carolin Franklin was married to Norman de Mattos Bentwich, who was Attorney General in the British Mandate of Palestine.[9] She was active in trade union organisation and women's suffrage, and was later a member of the London County Council.[10] [11]

Franklin was educated at St Paul's Girls' School and North London Collegiate School[12] [13] where she excelled in science, Latin[14] and sports.[15] Her family was actively involved with a Working Men's College, where Ellis Franklin, her father, taught electricity, magnetism and the history of the Great War in the evenings and later became vice principal.[16] [17] Later Franklin's family helped settle Jewish refugees from Europe who had escaped the Nazis.[11]

In the winter of 1938 Franklin went to Newnham College, Cambridge. She passed her finals in 1941, but was only awarded a degree titular, as women were not entitled to degrees (BA Cantab.) from Cambridge at the time; in 1945 Franklin received her PhD from Cambridge University.[18]

British Coal Utilisation Research Association

Franklin worked for Ronald Norrish between 1941 and 1942. Because of her desire to contribute to the World War II effort, she worked at the British Coal Utilisation Research Association in Kingston-upon-Thames from August 1942, studying the porosity of coal. Her work helped spark the idea of high-strength carbon fibres and was the basis of her 1945 doctoral thesis – "The physical chemistry of solid organic colloids with special reference to coal and related materials".[19] [20]

King's College London

Double Helix Discovery

William Astbury

Oswald Avery

Francis Crick

Erwin Chargaff

Max Delbrück

Jerry Donohue

Rosalind Franklin

Raymond Gosling

Phoebus Levene

Linus Pauling

Sir John Randall

Erwin Schrödinger

Alex Stokes

James Watson

Maurice Wilkins

Herbert Wilson

In January 1951, Franklin started working as a research associate at King's College London in the Medical Research Council's (MRC) Biophysics Unit, directed by John Randall.[21] Although originally she was to have worked on x-ray diffraction of proteins and lipids in solution, Randall redirected her work to DNA fibers before she started working at King's since Franklin was to be the only experienced experimental diffraction researcher at King's in 1951.[22] [23] He made this reassignment, even before she started working at King's, because of the following pioneering work by Maurice Wilkins and Raymond Gosling.[24] Even using crude equipment these two men had obtained an outstanding diffraction picture of DNA which sparked further interest in this molecule. Wilkins and Gosling had been carrying out x-ray diffraction analysis of DNA in the Unit since May 1950, but Randall had not informed them of his having asked Franklin to take over both the DNA diffraction work and guidance of Gosling's thesis.[25] Randall's lack of communication about this reassignment significantly contributed to the well documented friction that developed between Wilkins and Franklin.[26]

Franklin, working with her student Raymond Gosling,[27] started to apply her expertise in x-ray diffraction techniques to the structure of DNA. She used a new fine focus x-ray tube and microcamera ordered by Wilkins, but which she refined, adjusted and focused carefully. Drawing upon her physical chemistry background, Franklin also skillfully manipulated the critical hydration of her specimens.[28] When Wilkins inquired about this improved technique, Franklin replied in terms which offended Wilkins as Franklin had "an air of cool superiority".[29] Franklin's habit of intensely looking people in the eye while being concise, impatient and directly confrontational to the point of abrasiveness unnerved many of her colleagues. In stark contrast, Wilkins was very shy, and slowly calculating in speech while he avoided looking anyone directly in the eye.[30] In spite of the intense atmosphere, Franklin and Gosling discovered that there were two forms of DNA: at high humidity (when wet) the DNA fibre became long and thin, when it was dried it became short and fat.[31] [32] These were termed DNA 'B' and 'A' respectively. Because of the intense personality conflict developing between Franklin and Wilkins, Randall[33] divided the work on DNA. Franklin chose the data rich A form while Wilkins selected the 'B' form[34] [35] because his preliminary pictures had hinted it might be helical. He showed tremendous insight in this assessment of preliminary data. The x-ray diffraction pictures taken by Franklin at this time have been called, by J. D. Bernal, "amongst the most beautiful x-ray photographs of any substance ever taken".[31]

By the end of 1951 it was generally accepted in King's that the B form of DNA was a helix, but Franklin became unconvinced that the A form of DNA was helical in structure[36] after she had recorded an asymmetrical image in 1952 May. As a practical joke on Wilkins (who frequently expressed his view that DNA was helical), Franklin and Gosling produced a death notice regretting the 'death' of helical crystalline DNA (A-DNA).[37] During 1952 Rosalind Franklin and Raymond Gosling worked at applying the Patterson function to the x-ray pictures of DNA they had produced.[38] This was a long and labour-intensive approach but would yield significant insight into the structure of the molecule.[39] [40]
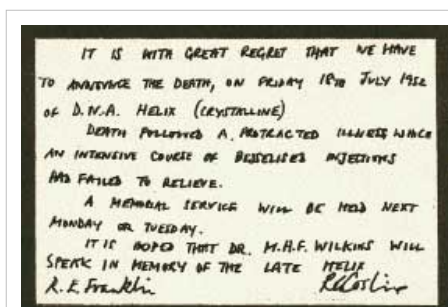
Franklin and Gosling death notice for a helical structure for crystalline DNA (or A-DNA)

By January 1953, Franklin had reconciled her conflicting data and had started to write a series of three draft manuscripts, two of which included a double helical DNA backbone (see below). Her two A form manuscripts reached Acta Crystallographica in Copenhagen on 6 March 1953,[41] one day before Crick and Watson had completed their model.[42] Franklin had to have mailed them while the Cambridge team was building their model, and certainly had written them before she knew of their work. On 8 July, 1953 she modified one of these "in proof", Acta articles "in light of recent work" by the King's and Cambridge research teams.[43] The third draft paper on the 'B' form of DNA, dated 17 January 1953, was discovered years later amongst her papers, by Franklin's Birkbeck colleague, Aaron Klug. He then published an evaluation of the draft's close correlation with the third of the original trio of 25 April 1953 *Nature* DNA articles.[44] Klug designed this paper to complement the first article he had written defending Franklin's significant contribution to DNA structure.[45] He had written this first article in response to the incomplete picture of Franklin's work depicted in Watson's 1968 memoir, *The Double Helix*.

As vividly described in *The Double Helix*, on 30 January 1953, Watson traveled to King's carrying a preprint of Linus Pauling's incorrect proposal for DNA structure. Since Wilkins was not in his office, Watson went to Franklin's lab with his urgent message that they should all collaborate before Pauling discovered his error. The unimpressed Franklin became angry when Watson suggested she did not know how to interpret her own data. Watson hastily retreated, backing into Wilkins who had been attracted by the commotion. Wilkins commiserated with his harried friend and then changed the course of DNA history with the following disclosure. Watson was shown (by Wilkins) Franklin's famous photograph 51, which had been given to Wilkins by Gosling. Watson, in turn, showed Wilkins a pre-publication manuscript by Pauling and Corey.[46] Franklin and Gosling's photo 51 gave the Cambridge pair critical insights into the DNA structure, whereas Pauling and Corey's paper described a molecule remarkably like their first incorrect model.

In February 1953 Francis Crick and James D. Watson of the Cavendish Laboratory in Cambridge University had started to build a model of the B form of DNA using similar data to that available to both teams at King's. Much of their data were derived directly from research done at King's by Wilkins and Franklin, with Franklin's being the most unique and critical data completed by February 1953.[47] Model building had been applied successfully in the elucidation of the structure of the alpha helix by Linus Pauling in 1951,[34] [48] but Franklin was opposed to prematurely building theoretical models, until sufficient data was obtained properly to guide the model building. She took the view that building a model was to be undertaken only after enough of the structure was known.[36] [49] Ever cautious she wanted to eliminate misleading possibilities. Photographs of her Birkbeck work table[50] show that she routinely used small molecular models, although certainly not ones on the grand scale successfully used at Cambridge for DNA. In the middle of February 1953, Crick's thesis advisor, Max Perutz gave Crick a copy of a report written for a Medical Research Council biophysics committee visit to King's in December 1952, containing many of Franklin's crystallographic calculations.[51] Since Franklin had decided to transfer to Birkbeck College and Randall had insisted that all DNA work must stay at King's, Wilkins was given copies of Franklin's diffraction photographs by Gosling. By 28 February 1953 Watson and Crick felt they had solved the problem enough for Crick to proclaim (in the local pub) that they had "found the secret of life".[52] However they knew they must complete their model before they could be certain.[53]

Watson and Crick finished building their model on 7 March 1953, one day before they received a letter from Wilkins stating that Franklin was finally leaving and they could put "all hands to the pump".[54] This was also one day after Franklin's two A form papers had reached Acta Crystallogrphica. Wilkins came to see the model the following week, according to Maddox on 12 March, and allegedly informed Gosling on his return to King's.[55] It is uncertain how

long it took for Gosling to inform Franklin at Birkbeck, but her original 17 March B form manuscript does not reflect any knowledge of the Cambridge model. Franklin did modify this draft later before publishing it as the third in the trio of 25 April 1953 *Nature* articles. On 18 March,[56] in response to receiving a copy of their preliminary manuscript, Wilkins penned the following "I think you're a couple of old rogues, but you may well have something".[57]

Crick and Watson then published their model in *Nature* on 25 April 1953 in an article describing the double-helical structure of DNA with only a footnote acknowledging "having been stimulated by a general knowledge of" Franklin and Wilkin's 'unpublished' contribution.[58] Actually, although it was the bare minimum, they had just enough specific knowledge of Franklin and Gosling's data upon which to base their model. As a result of a deal struck by the two laboratory directors, articles by Wilkins and Franklin, which included their x-ray diffraction data, were modified and then published second and third in the same issue of *Nature*, seemingly only in supported of the Crick and Watson theoretical paper which proposed a model for the B form of DNA.[59] [60] Franklin left King's College London in March 1953 to move to Birkbeck College in a move that had been planned for some time.[38]

Weeks later, on 10 April, Franklin wrote to Crick for permission to see their model.[61] Franklin retained her scepticism for premature model building even after seeing the Crick–Watson model, and remained unimpressed. She is reported to have commented, "It's very pretty, but how are they going to prove it?" As an experimental scientist Franklin seems to have been interested in producing far greater evidence before publishing-as-proven a proposed model. As such her response to the Crick–Watson model was in keeping with her cautious approach to science.[62] However, as documented above, she did not hesitate to publish preliminary ideas about DNA in ACTA, even before they could be definitively proven. Most of the scientific community hesitated several years before accepting the double helix proposal. At first mainly geneticists embraced the model because of its obvious genetic implications. Broader acceptance for the DNA double helix did not start until about 1960, and was not openly acknowledged until 1961 during the 1962 Nobel prize nominations. It took Wilkins and his colleagues approximately seven years to collect enough data to prove and refine the proposed DNA structure. According to the 1961 Crick–Monod letter cited above, this experimental proof, along with Wilkins having initiated the DNA diffraction work, were the reasons why Crick felt that Wilkins should be included in the DNA Nobel prize.

Birkbeck College

Franklin's work in Birkbeck involved the use of x-ray crystallography to study the structure of the tobacco mosaic virus (TMV) as a senior scientist with her own research group, funded by the Agricultural Research Council (ARC).[63] . She was recruited by physics department chair J. D. Bernal[64] , a brilliant crystallographer who happened to be an Irish communist, known for promoting women crystallographers. In 1954 Franklin began a longstanding and successful collaboration with Aaron Klug.[65] In 1955 Franklin had a paper published in the journal *Nature*, indicating that TMV virus particles were all of the same length,[66] this was in direct contradiction to the ideas of the eminent virologist Norman Pirie, though her observation ultimately proved correct.[67]

0.2 µm
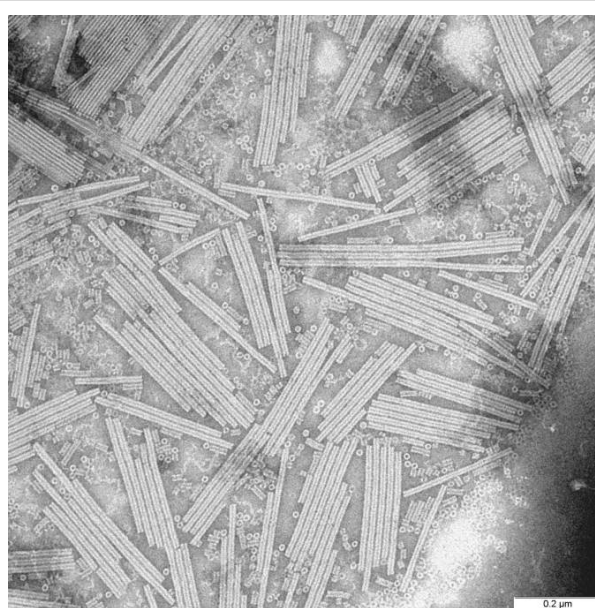
Electronmicrograph of Tobacco Mosaic Virus

Franklin, and the research group she headed, focused on the structure of RNA, a molecule equally central to life as DNA. RNA actually constitutes the genome (central information molecule) of many viruses, including tobacco mosaic virus. She assigned the study of rod-like viruses such as TMV (tobacco mosaic virus) to her PhD student Kenneth Holmes, while her colleague Aaron Klug worked on spherical viruses with his student John Finch, with Franklin coordinating and overseeing the work.[68] Franklin also had a research assistant, James Watt, subsidised by the National Coal Board and was now the *Leader of the "ARC group at Birkbeck*.[69] By the end of 1955 her team had completed a model of the TMV, to be exhibited at the upcoming Brussels World's fair. The Birkbeck team members were working on RNA viruses affecting several plants, including potato, turnip, tomato and pea.[70] Franklin and Don Caspar produced a paper each in *Nature* that taken together demonstrated that the DNA in TMV is wound along the inner surface of the hollow virus.[71] [72]

Her former colleagues at Birkbeck College, London Aaron Klug, John Finch and Kenneth Holmes moved to the Laboratory of Molecular Biology, Cambridge in 1962.

Illness and death

In the summer of 1956, while on a work-related trip to the United States, Franklin first began to suspect a health problem.[73] An operation in September of the same year revealed two tumours in her abdomen.[74] After this period and other periods of hospitalization, Franklin spent time convalescing with various friends and family members. These included Anne Sayre, Francis Crick, his wife Odile, with whom Franklin had formed a strong friendship,[75] and finally with the Roland and Nina Franklin family where Rosalind's nieces and nephews bolstered her spirits. Franklin chose not to stay with her parents because her mother's uncontrollable grief and crying upset her too much. Even while undergoing cancer treatment, Franklin continued to work, and her group continued to produce results, seven papers in 1956 and a further six in 1957.[76] In 1957, the group was also working on the polio virus and had obtained funding from the Public Health Service of the National Institutes of Health in the United States for this.[77] At the end of 1957, Franklin again fell ill and she was admitted to the Royal Marsden Hospital. She returned to work in January 1958 and she was given a promotion to *Research Associate in Biophysics*.[78] She fell ill again on March 30 and died on April 16, 1958, in Chelsea, London,[79] [80] of bronchopneumonia, secondary carcinomatosis and carcinoma of the ovary. Exposure to X-ray radiation is sometimes considered a possible factor in her illness. Other members of her family have died of cancer, and the incidence of "female" cancer is known to be disproportionately high among Ashkenazi Jews.[81] Her death certificate read: *A Research Scientist, Spinster, Daughter of Ellis Arthur Franklin, a Banker.*[82]

Controversies after death

Various controversies surrounding Rosalind Franklin came to light following her death.

Sexism at King's College

Rosalind Franklin worked in a research community that acknowledged women as scientists, but was infused with both conscious and unconscious sexism.[7] This sexism pervades Watson's memoir, *The Double Helix*, in which he denigrates her work and frequently refers to her in patronizing terms as "Rosy", a name she never used. Much later, Francis Crick acknowledges, "I'm afraid we always used to adopt--let's say, a *patronizing* attitude towards her". Cambridge colleague Peter Cavendish wrote in a letter, "Wilkins is supposed to be doing this work; Miss Franklin is evidently a fool". The one laboratory director who supposedly supported her, John Randall, pointedly told her to "cease to work on the nucleic acid problem" upon her departure from King's.[7]

The 1975 biography of Franklin by Anne Sayre (a friend who actually knew Franklin) asserted that Rosalind Franklin was discriminated against because of her gender and that King's, as an institution, was sexist. Among the examples cited in alleging sexist treatment at King's was that while "the male staff at King's lunched in a large, comfortable, rather clubby dining room" the female staff of all ranks "lunched in the student's hall or away from the

premises".[83] [84] Others recall differently that most of the MRC group typically ate lunch together (including Franklin) in the mixed dining room discussed below.[85] There was a dining room for the exclusive use of men (as was the case at other University of London colleges at the time), as well as a mixed-gender dining room that overlooked the River Thames, and many male scientists reportedly refused to use the male-only dining room owing to the preponderance of theologians.[86]

Another accusation regarding gender is that the under-representation of women in John Randall's group where only one participant was a woman was due to unfair exclusion.[87] In contrast, defenders of the King's College MRC group argue that women were (by the standards of the time) well-represented in the group, representing eight out of thirty-one members of staff,[88] or possibly closer to one in three,[89] although most were not senior scientists.[90]

Contribution to the model of DNA

Rosalind Franklin's critical contributions to the Crick and Watson model include an X-ray photograph of B-DNA (called photograph 51),[91] that was briefly shown to James Watson by Maurice Wilkins in January 1953,[92] [93] and a report written for an MRC biophysics committee visit to King's in December 1952 which was shown by Dr. Max Perutz at the Cavendish Laboratory to both Crick and Watson. This MRC report contained data from the King's group, including some of Rosalind Franklin's and Raymond Gosling's work, and was given to Francis Crick — who was working on his thesis on haemoglobin structure — by his thesis supervisor Max Perutz, a member of the visiting committee.[94] [95] Maurice Wilkins had been given photograph 51 by Rosalind Franklin's Ph.D. student Raymond Gosling, because she was leaving King's to work at Birkbeck. There was allegedly nothing untoward in this transfer of data to Wilkins,[96] [97] since the Director John Randall had insisted that all DNA work belonged exclusively to King's and had instructed Franklin in a letter to even stop thinking about it.[98] Also it was implied by Horace Freeland Judson, incorrectly, that Maurice Wilkins had taken the photograph out of Rosalind Franklin's drawer[99] . However, the B-DNA X-ray pattern photograph in question was shown to Watson by Wilkins — without Franklin's permission. Likewise Max Perutz saw "no harm" in showing an MRC report containing the conclusions of Franklin and Gosling's X-ray data analysis to Crick, since it had not been marked as confidential, although − in the customary British manner in which everything official is considered secret until it is deliberately made public − the report was not expected to reach outside eyes".[100] Indeed after the publication of Watson's *The Double Helix* exposed Perutz's act, he received so many letters questioning his judgement that he felt the need to both answer them all[101] and to post a general statement in *Science* excusing himself on the basis of being "inexperienced and casual in administrative matters".[102] Perutz also claimed that the MRC information was already made available to the Cambridge team when Watson had attended Franklin's seminar in November 1951. A preliminary version of much of the important material contained in the 1952 December MRC report had been presented by Franklin in a talk she had given in 1951 November, which Dr. Watson had attended but not understood.[103] [104] The Perutz letter was one of three letters, published with letters by Wilkins and Watson, which discussed their various contributions. Watson clarified the importance of the data obtained from the MRC report as he had not recorded these data while attending Franklin's lecture in 1951. The upshot of all this was that when Crick and Watson started to build their model in February 1953 they were working with critical parameters that had been determined by Franklin in 1951, and which she and Gosling had significantly refined in 1952, as well as with published data and other very similar data to those available at King's. Rosalind Franklin was probably never aware that her work had been used during construction of the model,[105] but Maurice Wilkins was.

Recognition of her contribution to the model of DNA

On the completion of their model, Francis Crick and James Watson had invited Maurice Wilkins to be a co-author of their paper describing the structure.[106] [107] Wilkins turned down this offer, as he had taken no part in building the model.[108] Maurice Wilkins later expressed regret that greater discussion of co-authorship had not taken place as this might have helped to clarify the contribution the work at King's had made to the discovery.[109] There is no doubt that Franklin's experimental data were used by Crick and Watson to build their model of DNA in 1953 (see above). Some, including Maddox as cited next, have explained this citation omission by suggesting that it may be a question of circumstance, because it would have been very difficult to cite the unpublished work from the MRC report they had seen.[110] Indeed a clear timely acknowledgment would have been awkward, given the unorthodox manner in which data was transferred from King's to Cambridge, however methods were available. Watson and Crick could have cited the MRC report as a personal communication or else cited the ACTA articles in press, or most easily, the third Nature paper that they knew was in press. One of the most important accomplishments of Maddox's widely acclaimed biography is that Maddox made a well-received case for inadequate acknowledgement. "Such acknowledgement as they gave her was very muted and always coupled with the name of Wilkins".[111]

Twenty five years after the fact, the first clear recitation of Franklin's contribution appeared as it permeated Watson's account, *The Double Helix*, although it was buried under allegations that Franklin did not know how to interpret her own data and that she should have therefore shared her work with Wilkins, Watson, and Crick. This attitude is epitomized in the confrontation between Watson and Franklin over a pre-print of Pauling's mistaken DNA manuscript.[112] Watson's words impelled Sayre to write her rebuttal, in which she designs her entire chapter nine, "Winner Take All" to be like a legal brief dissecting and analyzing the topic of acknowledgment.[113] Unfortunately Sayre's early analysis was often ignored because of the supposed feminist overtones in her book. It should be noted that in their original paper, Watson and Crick do cite the X-ray diffraction work of both Wilkins and William Astbury. In addition, they admit their, "having been stimulated by a knowledge of the general nature of the unpublished experimental work of [groups led by both both Wilkins and Franklin]".[2] Franklin and Raymond Gosling's own publication in the same issue of *Nature* was the first publication of this more clarified X-ray image of DNA.[114]

Nobel Prize

The rules of the Nobel Prize forbid posthumous nominations[107] and because Rosalind Franklin had died in 1958 she was not eligible for nomination to the Nobel Prize subsequently awarded to Crick, Watson, and Wilkins in 1962.[115] The award was for their body of work on nucleic acids and not exclusively for the discovery of the structure of DNA.[116] By the time of the award Wilkins had been working on the structure of DNA for over 10 years, and had done much to confirm the Watson-Crick model.[117] Crick had been working on the genetic code at Cambridge and Watson had worked on RNA for some years.[118]

Posthumous recognition

- 1982, Iota Sigma Pi designated Franklin a National Honorary Member.[119]
- 1992, English Heritage placed a blue plaque on the house Rosalind Franklin grew up in.[120]
- 1993, King's College London rename the Orchard Residence at their Hampstead Campus on Kidderpore Avenue Rosalind Franklin Hall.
- 1995, Newnham College dedicated a residence in her name and put a bust of her in its garden.[120]

Rosalind Franklin University of Medicine and Science

- 1997, Birkbeck, University of London School of Crystallography opened the Rosalind Franklin laboratory.[121]
- 1998, National Portrait Gallery added Rosalind Franklin's next to those of Francis Crick, James Watson and Maurice Wilkins.[120] [122]
- 2000, King's College London opened the Franklin-Wilkins Building in honour of Dr. Franklin's and Professor Wilkins' work at the college.[123] King's had earlier, in 1994, also named one of the Halls in Hampstead Campus residences in memory of Rosalind Franklin.
- 2001, The U.S. National Cancer Institute established the Rosalind E. Franklin Award for Women in Science.[124]
- 2003, the Royal Society established the Rosalind Franklin Award, for an outstanding contribution to any area of natural science, engineering or technology.[125]
- 2004, Finch University of Health Sciences/The Chicago Medical School, located in North Chicago, IL, changed its name to Rosalind Franklin University of Medicine and Science.[126]
- 2004, The University of Groningen, The Netherlands installed Rosalind Franklin fellowships to promote the hiring of young, promising, female researchers.
- 2005, the wording on the DNA sculpture (which was donated by James Watson) outside Clare College's Thirkill Court, Cambridge, UK is a) on the base: i) "These strands unravel during cell reproduction. Genes are encoded in the sequence of bases." and ii) *The double helix model was supported by the work of Rosalind Franklin and Maurice Wilkins."*, as well as b) on the helices: i) "The structure of DNA was discovered in 1953 by Francis Crick and James Watson while Watson lived here at Clare." and ii) "The molecule of DNA has two helical strands that are linked by base pairs Adenine − Thymine or Guanine − Cytosine." [127]
- 2008, Columbia University awarded an Honorary Horwitz Prize to Rosalind Franklin, Ph.D., posthumously, "for her seminal contributions to the discovery of the structure of DNA".[128]

References

- Bryson, B. *A Short History of Nearly Everything.* (2004). Black Swan ISBN 0-552-99704-8.
- Crick, F., H., C. and Watson, J., D. *Molecular structure of nucleic acids* [129] (1953) *Nature 171* pp. 737–738.
- Crick, F. H. C. *What Mad Pursuit*, (1988). Basic Books. ISBN 0-465-09137-7.
- Elkin, L., O. *Rosalind Franklin and the Double Helix* [130] *Physics Today* March 2003, pp. 42–48.
- Franklin RE (January 1950). "Influence of the bonding electrons on the scattering of X-rays by carbon". *Nature* **165** (4185): 71. PMID 15403103 [131].
- Ferry, Georgina, 2007. Max Perutz and the Secret of Life. Published in the UK by Chatto & Windus (ISBN 0-701-17695-4), and in the USA by the Cold Spring Harbor Laboratory Press.
- Franklin, R and Gosling, R., G. *Molecular Configuration in Sodium Thymonucleate Nature* volume *171* pages 740–741. (1953)full text [132].

- Franklin, R.E. and Gosling, R.G. authors of papers received 6 March 1953: Acta Cryst. (1953). 6, 673 The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content II. The Cylindrically Symmetrical Patterson Function
- Franklin, R.E. "Structure of tobacco mosaic virus." *Nature 175*:379–381 (1955).
- Franklin, R.E. (1956) "Location of the ribonucleic acid in the tobacco mosaic virus particle." *Nature 177*:928.
- Holt, J. (2002) "Photo Finish: Rosalind Franklin and the great DNA race [133]" *The New Yorker* October
- Judson, Horace Freeland, "The Eighth Day of Creation:Makers of the Revolution in Biology" (London: Jonathan Cape,1979),Penguin,1995;expanded edition;New York:Cold Spring Harbor Press,1996).
- Maddox, B. *Rosalind Franklin: The Dark Lady of DNA* (2002). Harper Collins ISBN 0-00-655211-0.
- Nobel Prize (1962). *The Nobel Prize in Physiology or Medicine 1962* [134], *for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material*, Nobelprize.org [135]
- Olby, R., "The Path to the Double Helix"(London:Macmillan,1974)
- Sayre, A. 1975. *Rosalind Franklin and DNA*. New York: W.W. Norton and Company. ISBN 0-393-32044-8.
- Segev, T. *One Palestine, Complete*, (2000) (ISBN 0-349-11286-X) Abacus History.
- Stent, Gunther, editor. "Critical Edition of The Double Helix"(1980) W.W. Norton Co, New York and London. ISBN 0-393-95075-1.
- Watson, J. Letter to *Science*, *164*, p. 1539, 27 (1969).
- Wilkins, M., *The Third Man of the Double Helix, an autobiography* (2003) Oxford University Press, Oxford. ISBN 0-19-280667-X.
- Yockey, H. P. *Information Theory, Evolution, and the Origin of Life* (2005).

Further reading

- Brown, Andrew; "*J. D. Bernal: The Sage of Science*", Oxford University Press, 2005; ISBN 0-199-20565-5
- Chomet, S. (Ed.), *D.N.A. Genesis of a Discovery*. Newman-Hemisphere Press (1994): NB a few copies are available from Newman-Hemisphere at 101 Swan Court, London SW3 5RY (phone/fax: 07092 060530).
- Crick, Francis (1988) "What Mad Pursuit: A Personal View of Scientific Discovery" (Basic Books reprint edition, 1990) ISBN 0-465-09138-5
- Dickerson, Richard E.; *"Present at the Flood: How Structural Molecular Biology Came About",* Sinauer, 2005; ISBN 0-878-93168-6
- John Finch; 'A Nobel Fellow On Every Floor', Medical Research Council 2008, 381 pp, ISBN 978-1840469-40-0; this book is all about the MRC Laboratory of Molecular Biology, Cambridge
- Hager, Thomas; "*Force of Nature: The Life of Linus Pauling*", Simon & Schuster 1995; ISBN 0-684-80909-5
- Freeland Judson, Horace (1996) [1977]. *The Eighth Day of Creation: Makers of the Revolution in Biology* (Expanded edition ed.). Plainview, N.Y: CSHL Press. ISBN 0-87969-478-5.
- Glynn, Jennifer Franklin. "Rosalind Franklin, 1920 – 1958" in "Cambridge Women: Twelve Portraits" (CUP 1996) pp 267 – 282 eds. Edward Shils and Carmen Blacker, ISBN 0521482879
- Klug, A. Oxford Dictionary of National Biography article on R.E. Franklin, OUP, Matthew H.C.G. Ed., first published Sept 2004; online edn, Jan 2007, 1840 words; ISBN 019861411X; was selected "Life of The Day" on 16 April 2008 (50th anniversary of her death).
- Klug, A. A lecture about Rosalind Franklin's contribution to the elucidation of the structure of DNA. in *DNA Changing Science and Society: The Darwin Lectures for 2003* Krude, Torsten (Ed.) CUP (2003)
- Olby, Robert, (1972) 'Rosalind Elsie Franklin' biography in "Dictionary of Scientific Biography", ed. Charles C. Gillespie (New York: Charles Scribner's sons) ISBN: ISBN 0684101211
- Olby, Robert, *The Path to The Double Helix: Discovery of DNA*, (1974). MacMillan ISBN 0-486-68117-3
- "Quiet debut for the double helix" [87] by Professor Robert Olby, *Nature 421* (January 23, 2003): 402–405.
- Tait, Sylvia & James "A Quartet of Unlikely Discoveries" (Athena Press 2004) ISBN 184401343X

- Watson, James D. (1980). *The double helix: A personal account of the discovery of the structure of DNA*. Norton. ISBN 0-393-01245-X.
- Wilkins, Maurice, "The Third Man of The Double Helix", OUP 2003; ISBN 978-0-19-280667-3.

External links

- Rosalind Franklin in CWP at UCLA [136]
- Himetop – The History of medicine topographical database in http://himetop.wikidot.com/rosalind-franklin
- The People's Archive: Sir Aaron Klug – see part 2, stories 12/13/17/18 re. Rosalind Franklin and:
- [137] Work at Birbeck and meeting REF (12)
- [138] Work with REF (13)
- [139] REF and the discovery of the structure of DNA. (17)
- [140] REF's death and joining the MRC's LMB in Cambridge (18)

Articles

Franklin, S.*My aunt, the DNA pioneer [141]

- Elkin, L.O. "Rosalind Franklin and the Double Helix" in "Physics Today" magazine [130]

Piper, A.*Light on a Dark Lady [142], republished article from *Trends in Biochemical Science*

- Oxford Dictionary of National Biography for article by Sir Aaron Klug [143]
- [144] The first American newspaper coverage of the discovery of the DNA structure: Saturday, June 13, 1953 The New York Times
- Lynne Elkin, Biography of Rosalind Franklin [145], Jewish Women Encyclopedia

Documentaries

- *Nova*: "Secret of Photo 51" [146]

Collections and publications

- The Rosalind Franklin Society [147].
- The Rosalind Franklin Papers [148] at the National Library of Medicine
- Anne Sayre Collection [149] of Rosalind Franklin Materials
- Lynne Elkin collection of original Franklin research at the Bancroft Archive of the University of California, Berkeley [150]
- The Rosalind Franklin Papers [151] at Churchill Archives Centre in Cambridge.
- Key Participants: Rosalind Franklin [152] – *Linus Pauling and the Race for DNA: A Documentary History*
- "Rosalind Franklin's work on coal, carbon, and graphite", by Peter J F Harris [153] in PDF format
- Energia Vol.6 No.6 (1995) (University of Kentucky centre for Applied Energy Research). Contains Rosalind Franklin Article [154] in PDF format
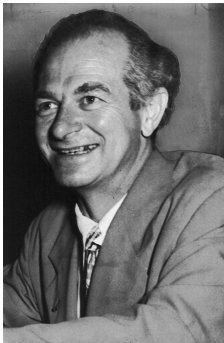
References

[1] Crick's 31 December 1961 letter to Jacques Monod was discovered in the Archives of the Pasteur Institute by Doris Zeller, then reprinted in "Nature Correspondence" 425, 15 on the 4th of September 2003. Watson confirmed this opinion in his own statement at the opening of the King's college Franklin-Wilkins building in 2000.

[2] Watson JD, Crick FHC (1953). "A Structure for Deoxyribose Nucleic Acid". *Nature 171*: 737–738. Full text PDF (http://www.nature.com/nature/dna50/watsoncrick.pdf) This article was immediately followed by the two King's submissions: M.H.F. Wilkins, A.R. Stokes, and H.R. Wilson. Molecular Structure of Deoxypentose Nucleic Acids, pp738–740 then by: Rosalind E. Franklin and R.G. Gosling. Molecular configuration of Sodium Thymonucleate pp 740–741.

[3] *Double Helix: 50 Years of DNA*. Nature archives. Nature Publishing Group (http://www.nature.com/nature/dna50/archive.html)

[4] Watson, James D. The Double Helix: A personal Account of the Discovery of the Structure of DNA (New York:Athenium,1968;London:Weidenfeldand Nicolson, 1981)

[5] Consult references listed in order of publication: Olby, Sayre, Klug, Piper, Judson, Glynn, Maddox, Elkin

[6] GRO Register of Births: SEP 1920 1a 250 KENSINGTON – Rosalind E. Franklin, mmn = Waley

[7] Maddox, Brenda (2002). *Rosalind Franklin: The Dark Lady of DNA*. HarperCollins. ISBN 0060184078.

[8] Maddox p. 7

[9] Segev p.

[10] Sayre,A,. *Rosalind Franklin and DNA*(New York:Norton,1975). p. 31

[11] Maddox p. 40

[12] Maddox p. 25

[13] Sayre p. 41

[14] Maddox p. 30

[15] Maddox, p. 26

[16] Maddox, p. 20

[17] Sayre, p. 35

[18] http://www.lifeindiscovery.com/whyrosalindfranklin/index.html

[19] Maddox, pp.40–82

[20] Sayre pp. 47–57

[21] Maddox, p. 124

[22] Maddox, p. 114

[23] Wilkins, Wilkins, M., The Third Man of the Double Helix, an autobiography (2003) Oxford University Press, Oxford. pp. 143–144

[24] Wilkins, p. 121

[25] Maddox, pp. 149–150, Elkin, p 45. Elkin, L.O. Rosalind Franklin and the Double Helix. Physics Today, March 2003(available free on-line, see references). Olby, R. The Path to the Double Helix (London: MacMillan, 1974).

[26] Sayre, Olby, Maddox, Elkin, Wilkins

[27] Maddox, p. 129

[28] Elkin, p. 43

[29] Wilkins p. 155

[30] Elkin p. 45

[31] Maddox, p. 153

[32] Wilkins, p. 154

[33] Maddox p 155

[34] Wilkins, p. 158

[35] Maddox, p. 155

[36] Wilkins, p. 176

[37] Wilkins, p. 182

[38] Maddox, p. 168

[39] Maddox, p. 169

[40] Wilkins, pp. 232–233

[41] Franklin, R.E. and Gosling, R.G. authors of papers received 6 March 1953 Acta Cryst. (1953). 6, 673 The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content Acta Cryst. (1953). 6, 678 The Structure of Sodium Thymonucleate Fibres II. The Cylindrically Symmetrical Patterson Function

[42] Maddox p 205

[43] Acta Cryst. (1953). 6, 673 The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content

[44] Klug, A. "Rosalind Franklin and the Double Helix", Nature 248 (26 April 1974): 787–788

[45] Klug, A. Rosalind Franklin and the Discovery of the Structure of DNA, Nature 219 (24 August 1968): 808–810 & 843.

[46] Yockey, pp. 9–10

[47] Crick's 31 December 1961 letter to Jacque Monod cited above

[48] Maddox, p. 147

[49] Maddox, p. 161

[50] Photograph was taken in the same series of photographs taken by Franklin's colleague John Finch, as the one shown of Franklin's Birkbeck desk that was reproduced by Maddox. Author Lynne Elkin was given a complete set and was informed by Finch that he had given a complete set to Maddox.

[51] Hubbard, Ruth (1990). *The Politics of Women's Biology*. Rutgers State University. p. 60. ISBN 0-8135-1490-8.

[52] "The Double Helix" p. 115

[53] "The Double Helix" p. 60

[54] "All hands to the pump" letter is preserved in the Crick archives at the University of California, San Diego, and was posted as part of their Web collection. It is also quoted by both Maddox, p 204, and Olby.

[55] Maddox p. 207

[56] In contrast to his other letters to Crick, Wilkins dated this one.

[57] "Old rogues" letter is preserved in the Crick archives at the University of California at San Diego, and was posted as part of their Web collection. It is also quoted by both Maddox, p. 208 and Olby.

[58] Maddox, p. 212

[59] Franklin and Gosling (1953)

[60] Maddox, p. 210

[61] 10 April 1953 Franklin post card to Crick asking permission to view model. The original is in the Crick archives at the University of California, San Diego.

[62] Holt, J. (2002)

[63] Maddox, p. 235

[64] Maddox, p. 229

[65] Maddox, p. 249

[66] Franklin (1955)

[67] Maddox, p. 252

[68] Maddox, p. 254

[69] Maddox, p. 256

[70] Maddox, p. 262

[71] Maddox, p. 269

[72] Franklin (1956)

[73] Maddox, p. 284

[74] Maddox, p. 285

[75] Maddox, p. 288

[76] Maddox, p. 292

[77] Maddox, p. 296

[78] Maddox, p. 302

[79] GRO Register of Deaths: JUN 1958 5c 257 CHELSEA – Rosalind E. Franklin, aged 37

[80] Maddox, pp. 305–307

[81] Maddox, p.320

[82] Maddox, p.307

[83] Sayre, p.97

[84] Bryson, B. (2004) p. 490

[85] Elkin, p.45

[86] Maddox, p. 128

[87] Sayre, p.99

[88] Maddox, p. 133

[89] Wilkins, p. 256

[90] Elkin, p45

[91] Maddox, pp. 177–178

[92] Maddox, p. 196

[93] Crick, (1988) p. 67.

[94] Elkin, L.O. (2003)p 44

[95] Maddox, pp. 198–199

[96] Maddox, pp. 196

[97] Wilkins, p. 198

[98] Maddox p.312,

[99] Wilkins, p. 257

[100] Maddox p.188

[101] Perutz's papers are in the Archive of the J. Craig Venter institute and Science Foundation in Rockville Maryland, which were purchased as part of the Jeremy Norman Archive of Molecular Biology; quoted in Ferry, Georgina, 2007. Max Perutz and the Secret of Life. Published in

the UK by Chatto & Windus (ISBN 0-701-17695-4), and in the USA by the Cold Spring Harbor Laboratory Press.

[102] "Science, 27 June, 1969, pp. 207–212, also reprinted in the Norton critical edition of *The Double Helix*, edited by Gunther Stent.

[103] Maddox, p. 199

[104] Watson (1969).

[105] Maddox, p. 316

[106] Wilkins, p. 213

[107] Maddox, p. 205

[108] Wilkins, p. 214

[109] Wilkins, p. 226

[110] Maddox, p. 207

[111] Maddox, pp316–317, and other parts of the epilogue

[112] Watson, J.D. (1968) pp. 95–96

[113] Sayre,A. (1975) pp. 156–167

[114] Franklin R, Gosling RG (1953) "Molecular Configuration in Sodium Thymonucleate". *Nature 171*: 740–741. Full text PDF (http://www.nature.com/nature/dna50/franklingosling.pdf)

[115] Nobel Prize (1962)

[116] Wilkins, p. 242

[117] Wilkins, p. 240

[118] Wilkins, p. 243

[119] Iota Sigma Pi professional awards recipients (http://www.iotasigmapi.info/ISPprofawards/ISPprofawardees.html)

[120] Maddox, p. 322

[121] *Sir Aaron Klug opens new Laboratory* (http://img.cryst.bbk.ac.uk/bca/CNews/1997/Sep97/Cover.html#Cover)

[122] NPG pictures (http://www.npg.org.uk/live/search/person.asp?search=ss&sText=Rosalind+Franklin&LinkID=mp58704)

[123] Maddox, p. 323

[124] "seventh annual Rosalind E. Franklin Award for Women in Cancer Research at the National Cancer Institute's Intramural Scientific Retreat [which] honors the commitment of women in cancer research and is given in tribute to chemist Rosalind Franklin, who played a critical role in the discovery of the DNA double helix." *The JHU Gazette*, Johns Hopkins University, March 17 2008 For the Record: Cheers (http://www.jhu.edu/~gazette/2008/17mar08/17cheers.html)

[125] [[The Royal Society (http://www.royalsoc.ac.uk/page.asp?id=1782)] Rosalind Franklin Award (2003)]: The Royal Society web page. Retrieved 21 July 2006.

[126] Dedication (http://www.lifeindiscovery.com/news/index.html) of Rosalind Franklin University (http://www.rosalindfranklin.edu/)

[127] http://www.cambridge-news.co.uk/cn_news_cambridge/displayarticle.asp?id=268669

[128] http://www.medicalnewstoday.com/articles/125564.php

[129] http://profiles.nlm.nih.gov/SC/B/B/Y/W/_/scbbyw.pdf

[130] http://scitation.aip.org/getpdf/servlet/GetPDFServlet?filetype=pdf&id=PHTOAD000056000003000042000001&idtype=cvips

[131] http://www.ncbi.nlm.nih.gov/pubmed/15403103

[132] http://www.nature.com/nature/dna50/franklingosling.pdf

[133] http://mcb.berkeley.edu/courses/mcb61/Photo_Finish_Rosalind_Franklin.doc

[134] http://nobelprize.org/medicine/laureates/1962/index.html

[135] http://nobelprize.org

[136] http://cwp.library.ucla.edu/Phase2/Franklin,_Rosalind@841234567.html

[137] http://peoplesarchive.com/browse/movies/7015/en/off/

[138] http://peoplesarchive.com/browse/movies/7017/en/off/

[139] http://peoplesarchive.com/browse/movies/7021/en/off/

[140] http://peoplesarchive.com/browse/movies/7022/en/off/

[141] http://news.bbc.co.uk/2/hi/science/nature/2895681.stm

[142] http://cwp.library.ucla.edu/articles/franklin/piper.html

[143] http://www.oxforddnb.com

[144] http://www.nytimes.com/packages/pdf/science/dna-article.pdf

[145] http://jwa.org/encyclopedia/article/franklin-rosalind

[146] http://www.pbs.org/wgbh/nova/photo51/

[147] http://www.rosalindfranklinsociety.org

[148] http://profiles.nlm.nih.gov/KR/

[149] http://www.asm.org/Membership/index.asp?bid=16414

[150] http://bancroft.berkeley.edu

[151] http://janus.lib.cam.ac.uk/db/node.xsp?id=EAD%2FGBR%2F0014%2FFRKN

[152] http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/people/franklin.html

[153] http://www.personal.rdg.ac.uk/~scsharip/REF_paper.pdf

[154] http://www.caer.uky.edu/energeia/PDF/vol6-6.pdf

Linus Pauling

Linus Pauling	
	 Linus Pauling in 1954
Born	28 February 1901 Portland, Oregon, USA
Died	19 August 1994 (aged 93) Big Sur, California, USA
Residence	United States
Nationality	American
Fields	Quantum chemistry Biochemistry
Institutions	Caltech, UCSD, Stanford
Alma mater	Oregon Agricultural College Caltech
Doctoral advisor	Roscoe G. Dickinson
Other academic advisors	Arnold Sommerfeld Erwin Schrödinger Niels Bohr
Doctoral students	Jerry Donohue Martin Karplus Matthew Meselson Edgar Bright Wilson William Lipscomb
Known for	Elucidating the nature of chemical bonds and the structures of molecules Advocating nuclear disarmament
Notable awards	Nobel Prize in Chemistry (1954) Nobel Peace Prize (1962) Lenin Peace Prize (1968-1969)
Notes The first person to win unshared Nobel Prizes in two different fields	

Linus Carl Pauling (February 28, 1901 – August 19, 1994) was an American chemist, peace activist, author, and educator. He was one of the most influential chemists in history and ranks among the most important scientists in any field of the 20th century[1] [2] . Pauling was among the first scientists to work in the fields of quantum chemistry, molecular biology, and orthomolecular medicine. He is one of only four individuals to have won multiple Nobel Prizes.[3] He is one of only two people to have been awarded a Nobel Prize in two different fields (the Chemistry and

Peace prizes), the other being Marie Curie (the Chemistry and Physics prizes), and the only person to have been awarded each of his prizes without sharing it with another recipient.[4]

Biography

Early years

Pauling was born in Portland, Oregon, as the first born child to Herman Henry William Pauling (1876–1910) and Lucy Isabelle "Belle" Darling (1881–1926).[5] He was named "Linus Carl", in honor of Lucy's father, Linus, and Herman's father, Carl.[6] Herman and Lucy—then 23 and 18 years old, respectively—had met at a dinner party in Condon. Six months later, the two were married.[7]

Herman Pauling descended from South-German farmers, who had immigrated to a German settlement in Concordia, Missouri. Carl Pauling moved his family to California before settling in Oswego. There, he worked as an ironmonger at a foundry.[8] After completing grammar school, Herman Pauling served as an apprentice to a druggist. Upon completion of his services, he became a wholesale drug salesman.[9]

Pauling's mother, Lucy, of Irish descent, was the daughter of Linus Wilson Darling, who had served as a teacher, farmer, surveyor, postmaster and lawyer at different points of his life. Linus Darling was

Herman Henry William Pauling c. 1900, Linus Pauling's father

orphaned at age 11 and apprenticed under a baker before becoming a schoolteacher. He fell in love with a young woman named Alice from Turner, Oregon, whom he eventually married.[10] On July 17, 1888, Alice gave birth to the couple's fifth child, but he was stillborn. Less than a month later, she died, leaving Darling to take care of their four young daughters.[11]

Linus Pauling spent his first year living in a one-room apartment with his parents in Portland. In 1902, after his sister Pauline was born, Pauling's parents decided to move out of the city.[12] They were crowded in their apartment, but couldn't afford more spacious living quarters in Portland. Lucy stayed with her husband's parents in Oswego, while Herman searched for new housing. Herman brought the family to Salem, where he took up a job as a traveling salesman for the Skidmore Drug Company. Within a year of Lucile's birth in 1904, Herman Pauling moved his family to Oswego, where he opened his own drugstore.[12] The business climate in Oswego was poor, so he moved his family to Condon in 1905.[13]

In 1909, Pauling's grandfather, Linus, divorced his second wife and married a young schoolteacher, almost the same age as his daughter Lucy. A few months later, he died of a heart attack, brought on by complications from nephritis.[14] Meanwhile, Herman Pauling was suffering from poor health and had regular sharp pains in his abdomen. Lucy's sister, Abbie, saw that Herman was dying and immediately called the family physician. The doctor gave Herman a sedative to reduce the pain, but it only offered temporary relief.[15] His health worsened in the coming months and finally died of a perforated ulcer on June 11, 1910, leaving Lucy to care for Linus, Lucile and Pauline.[16]

Linus was a voracious reader as a child, and at one point his father wrote a letter to *The Oregonian* inviting suggestions of additional books to occupy his time.[17] Pauling first planned to become a chemist after being amazed by experiments conducted with a small chemistry lab kit by his friend, Lloyd A. Jeffress.[18] In high school, Pauling continued to conduct chemistry experiments, borrowing much of the equipment and material from an abandoned steel plant. With an older friend, Lloyd Simon, Pauling set up Palmon Laboratories. Operating from Simon's

basement, the two young adults approached local dairies to offer their services in performing butterfat samplings at cheap prices. Dairymen were wary of trusting two young boys with the task, and as such, the business ended as a failure.[19]

By the fall of 1916, Pauling was a 15-year-old high school senior and had enough credits to enter Oregon Agricultural College (OAC, now known as Oregon State University) in Corvallis.[20] However, he did not have enough credits for two required American history courses that would satisfy his requirement to earn a high school diploma. He asked the school principal if he could take these courses concurrently during the spring semester. The principal denied his request, and Pauling decided to leave the school in June without a diploma.[21] His high school, Washington High School in Portland, awarded him the diploma 45 years later, after he had won two Nobel Prizes.[22] [23] During the summer, Pauling worked part-time at a grocery store, earning eight dollars a week. His mother set him up with an interview with a Mr. Schwietzerhoff, the owner of a number of manufacturing plants in Portland. Pauling was hired as an apprentice machinist with a salary of 40 dollars a month. Pauling excelled at his job, and saw his salary increase to 50 dollars a month after being on the job for only a month.[24] In his spare time, he set up a photography lab with two friends and found business from a local photography company. He hoped that the business would earn him enough money to pay for his future college expenses.[25] Pauling received a letter of admission from OAC in September 1917 and immediately gave notice to his boss and told his mother of his plans.[26]

Higher education

In October 1917, Pauling entered Oregon Agricultural College and lived in a boarding house on campus with his cousin Mervyn and another man, using the $200 he had saved from odd jobs to finance his education. In his first semester, Pauling registered for two courses in chemistry, two in mathematics, mechanical drawing, introduction to mining and use of explosives, modern English prose, gymnastics and military drill.[27] Pauling fell in love with a freshman girl named Irene early in the school year. By the end of October, he had used up $150 of his savings on her, taking her to shows and games. He soon got a job at the girls' dormitory, working 100 hours a month chopping wood for stoves, cutting up beef and mopping up the kitchen. Despite the 25 cent per hour salary, Pauling was still having trouble managing his finances. He began eating one hot meal a day at a restaurant off campus to minimize his expenses.[27] Pauling was active in campus life and founded the school's chapter of the Delta Upsilon fraternity.[28] After his second year, he planned to take a job in Portland to help support his mother, but the college offered him a position teaching quantitative analysis, a course he had just finished taking himself. He worked forty hours a week in the laboratory and classroom and earned $100 a month.[29] This allowed him to continue his studies at the college.

Pauling's graduation photo from Oregon Agricultural College in 1922

In his last two years at school, Pauling became aware of the work of Gilbert N. Lewis and Irving Langmuir on the electronic structure of atoms and their bonding to form molecules.[29] He decided to focus his research on how the physical and chemical properties of substances are related to the structure of the atoms of which they are composed, becoming one of the founders of the new science of quantum chemistry. Pauling began to neglect his studies in humanities and social sciences. He had also exhausted the course offerings in the physics and mathematics departments. Professor Samuel Graf selected Pauling to be his teaching assistant in a high-level mathematics course.[30] During the winter of his senior year, Pauling was approached by the college to teach a chemistry course for home economics majors. It was in one of these classes that Pauling met his future wife, Ava Helen Miller.[31]

In 1922, Pauling graduated from OAC with a degree in chemical engineering and went on to graduate school at the California Institute of Technology (Caltech) in Pasadena, California, under the guidance of Roscoe G. Dickinson. His graduate research involved the use of X-ray diffraction to determine the structure of crystals. He published seven papers on the crystal structure of minerals while he was at Caltech. He received his Ph. D. in physical chemistry and mathematical physics, *summa cum laude*, in 1925.

Personal life

During his senior year of college, Pauling taught a class called "Chemistry for Home Economic Majors".[32] In one of those classes, he met Ava Helen Miller from Beavercreek, whom he married on June 17, 1923. They had four children: Linus Carl Jr. (b. 1925); Peter Jeffress (1931–2003, a crystallographer and lecturer in chemistry); Edward Crellin (1937–1997, professor of biology at San Francisco State University and the University of California, Riverside), and Linda Helen, (b. 1932).

Pauling was raised as a member of the Lutheran Church, but later joined the Unitarian Universalist Church and publicly declared his atheism two years before his death.[33]

Career

Pauling had first been exposed to the concepts of quantum theory and quantum mechanics while he was studying at Oregon State University. He later traveled to Europe on a Guggenheim Fellowship, which was awarded to him in 1926, to study under German physicist Arnold Sommerfeld in Munich, Danish physicist Niels Bohr in Copenhagen, and Austrian physicist Erwin Schrödinger in Zürich. All three were experts working in the new field of quantum mechanics and other branches of physics. Pauling became interested in seeing how quantum mechanics might be applied in his chosen field of interest, the electronic structure of atoms and molecules. In Europe, Pauling was also exposed to one of the first quantum mechanical analyses of bonding in the hydrogen molecule, done by Walter Heitler and Fritz London. Pauling devoted the two years of his European trip to this work and decided to make it the focus of his future research. He became one of the first scientists in the field of quantum chemistry and a pioneer in the application of quantum theory to the structure of molecules. He also joined Alpha Chi Sigma, the professional chemistry fraternity.

In 1927, Pauling took a new position as an assistant professor at Caltech in theoretical chemistry. He launched his faculty career with a very productive five years, continuing with his X-ray crystal studies and also performing quantum mechanical calculations on atoms and molecules. He published approximately fifty papers in those five years, and created five rules now known as Pauling's Rules. By 1929, he was promoted to associate professor, and by 1930, to full professor. In 1931, the American Chemical Society awarded Pauling the Langmuir Prize for the most significant work in pure science by a person 30 years of age or younger.[34] The following year, Pauling published what he regarded as his most important paper, in which he first laid out the concept of hybridization of atomic orbitals and analyzed the tetravalency of the carbon atom.[35]

At Caltech, Pauling struck up a close friendship with theoretical physicist Robert Oppenheimer, who was spending part of his research and teaching schedule away from U.C. Berkeley at Caltech every year. The two men planned to mount a joint attack on the nature of the chemical bond: apparently Oppenheimer would supply the mathematics and Pauling would interpret the results. However, their relationship soured when Pauling began to suspect that Oppenheimer was becoming too close to Pauling's wife, Ava Helen. Once, when Pauling was at work, Oppenheimer had come to their place and blurted out an invitation to Ava Helen to join him on a tryst in Mexico.[36] Although she flatly refused, she reported the incident to Pauling. Disquieted by this strange chemistry, and her apparent nonchalance about the incident, he immediately cut off his relationship with Oppenheimer.

In the summer of 1930, Pauling made another European trip, during which he learned about the use of electrons in diffraction studies similar to the ones he had performed with X-rays. After returning, he built an electron diffraction instrument at Caltech with a student of his, L. O. Brockway, and used it to study the molecular structure of a large

number of chemical substances.

Pauling introduced the concept of electronegativity in 1932. Using the various properties of molecules, such as the energy required to break bonds and the dipole moments of molecules, he established a scale and an associated numerical value for most of the elements—the Pauling Electronegativity Scale—which is useful in predicting the nature of bonds between atoms in molecules.

Activism

Pauling had been practically apolitical until World War II, but the aftermath of the war and his wife's pacifism changed his life profoundly, and he became a peace activist. During the beginning of the Manhattan Project, Robert Oppenheimer invited him to be in charge of the Chemistry division of the project, but he declined, not wanting to uproot his family. He did work on other projects that had military applications such as explosives, rocket propellants, an oxygen meter for submarines and patented an armor piercing shell and was awarded a Presidential Medal of Merit.[37] [38] In 1946, he joined the Emergency Committee of Atomic Scientists, chaired by Albert Einstein.[39] Its mission was to warn the public of the dangers associated with the development of nuclear weapons. His political activism prompted the U.S. State Department to deny him a passport in 1952, when he was invited to speak at a scientific conference in London.[40] [41] His passport was restored in 1954, shortly before the ceremony in Stockholm where he received his first Nobel Prize. Joining Einstein, Bertrand Russell and eight other leading scientists and intellectuals, he signed the Russell-Einstein Manifesto in 1955.[42]

In 1958, Pauling joined a petition drive in cooperation with the founders of the St. Louis Citizen's Committee for Nuclear Information (CNI). This group, headed by Washington University professors Barry Commoner, Eric Reiss, M. W. Friedlander, and John Fowler, set up a study of radioactive strontium-90 in the baby teeth of children across North America. The "Baby Tooth Survey," headed by Dr. Louise Z. Reiss [43], demonstrated conclusively in 1961 that above-ground nuclear testing posed significant public health risks in the form of radioactive fallout spread primarily via milk from cows that had ingested contaminated grass.[44] [45] [46] Pauling also participated in a public debate with the atomic physicist Edward Teller about the actual probability of fallout causing mutations.[47] In 1958, Pauling and his wife presented the United Nations with the petition signed by more than 11,000 scientists calling for an end to nuclear-weapon testing. Public pressure and the frightening results of the CNI research subsequently led to a moratorium on above-ground nuclear weapons testing, followed by the Partial Test Ban Treaty, signed in 1963 by John F. Kennedy and Nikita Khrushchev. On the day that the treaty went into force, the Nobel Prize Committee awarded Pauling the Nobel Peace Prize, describing him as "Linus Carl Pauling, who ever since 1946 has campaigned ceaselessly, not only against nuclear weapons tests, not only against the spread of these armaments, not only against their very use, but against all warfare as a means of solving international conflicts."[48] The Committee for Nuclear Information was never credited for its significant contribution to the test ban, nor was the ground-breaking research conducted by Dr. Reiss and the "Baby Tooth Survey". The Caltech Chemistry Department, wary of his political views, did not even formally congratulate him. They did throw him a small party, showing they were more appreciative and sympathetic toward his work on radiation mutation. At Caltech he founded Sigma Xi's (The Scientific Research Society) chapter at the school, as he had previously been a member of that organisation. He continued his peace activism in the following years co-founding the International League of Humanists in 1974. He was president of the scientific advisory board of the World Union for Protection of Life and also one of the signers of the Dubrovnik-Philadelphia Statement.

Many of Pauling's critics, including scientists who appreciated the contributions that he had made in chemistry, disagreed with his political positions and saw him as a naive spokesman for Soviet communism. He was ordered to appear before the Senate Internal Security Subcommittee, which termed him "the number one scientific name in virtually every major activity of the Communist peace offensive in this country." An extraordinary headline in *Life* magazine characterized his 1962 Nobel Prize as "A Weird Insult from Norway". Pauling was awarded the International Lenin Peace Prize by the USSR in 1970.[49]

Biological molecules

Double Helix Discovery

William Astbury

Oswald Avery

Francis Crick

Erwin Chargaff

Max Delbrück

Jerry Donohue

Rosalind Franklin

Raymond Gosling

Phoebus Levene

Linus Pauling

Sir John Randall

Erwin Schrödinger

Alex Stokes

James Watson

Maurice Wilkins

Herbert Wilson

In the mid-1930s, Pauling, strongly influenced by the biologically oriented funding priorities of the Rockefeller Foundation's Warren Weaver, decided to strike out into new areas of interest. Although Pauling's early interest had focused almost exclusively on inorganic molecular structures, he had occasionally thought about molecules of biological importance, in part because of Caltech's growing strength in biology. Pauling interacted with such great biologists as Thomas Hunt Morgan, Theodosius Dobzhanski, Calvin Bridges, and Alfred Sturtevant. His early work in this area included studies of the structure of hemoglobin. He demonstrated that the hemoglobin molecule changes structure when it gains or loses an oxygen atom. As a result of this observation, he decided to conduct a more thorough study of protein structure in general. He returned to his earlier use of X-ray diffraction analysis. But protein structures were far less amenable to this technique than the crystalline minerals of his former work. The best X-ray pictures of proteins in the 1930s had been made by the British crystallographer William Astbury, but when Pauling tried, in 1937, to account for Astbury's observations quantum mechanically, he could not.

It took eleven years for Pauling to explain the problem: his mathematical analysis was correct, but Astbury's pictures were taken in such a way that the protein molecules were tilted from their expected positions. Pauling had formulated a model for the structure of hemoglobin in which atoms were arranged in a helical pattern, and applied this idea to proteins in general.

In 1951, based on the structures of amino acids and peptides and the planarity of the peptide bond, Pauling, Robert Corey, and Herman Branson correctly proposed the alpha helix and beta sheet as the primary structural motifs in protein secondary structure. This work exemplified Pauling's ability to think unconventionally; central to the

structure was the unorthodox assumption that one turn of the helix may well contain a non-integral number of amino acid residues.

Pauling then proposed that deoxyribonucleic acid (DNA) was a triple helix;[50] however, his model contained several basic mistakes, including a proposal of neutral phosphate groups, an idea that conflicted with the acidity of DNA. Sir Lawrence Bragg had been disappointed that Pauling had won the race to find the alpha helix structure of proteins. Bragg's team had made a fundamental error in making their models of protein by not recognizing the planar nature of the peptide bond. When it was learned at the Cavendish Laboratory that Pauling was working on molecular models of the structure of DNA, Watson and Crick were allowed to make a molecular model of DNA using unpublished data from Maurice Wilkins and Rosalind Franklin at King's College. Early in 1953 James D. Watson and Francis Crick proposed a correct structure for the DNA double helix. Pauling later cited several reasons to explain how he had been misled about the structure of DNA, among them misleading density data and the lack of high quality X-ray diffraction photographs. During the time Pauling was researching the problem, Rosalind Franklin in England was creating the world's best images. They were key to Watson's and Crick's success. Pauling did not see them before devising his mistaken DNA structure, although his assistant Robert Corey did see at least some of them, while taking Pauling's place at a summer 1952 protein conference in England. Pauling had been prevented from attending because his passport was withheld by the State Department on suspicion that he had Communist sympathies. This led to the legend that Pauling missed the structure of DNA because of the politics of the day (this was at the start of the McCarthy period in the United States).[51] Politics did not, however, play a critical role. Not only did Corey see the images at the time, but Pauling himself regained his passport within a few weeks and toured English laboratories well before writing his DNA paper. He had ample opportunity to visit Franklin's lab and see her work, but chose not to.[52]

Pauling also studied enzyme reactions and was among the first to point out that enzymes bring about reactions by stabilizing the transition state of the reaction, a view which is central to understanding their mechanism of action. He was also among the first scientists to postulate that the binding of antibodies to antigens would be due to a complementarity between their structures. Along the same lines, with the physicist turned biologist Max Delbruck, he wrote an early paper arguing that DNA replication was likely to be due to complementarity, rather than similarity, as suggested by a few researchers. This was made clear in the model of the structure of DNA that Watson and Crick discovered.

Molecular genetics

In November 1949, Linus Pauling, Harvey Itano, S. J. Singer and Ibert Wells published "Sickle Cell Anemia, a Molecular Disease"[53] in the journal *Science*. It was the first proof of a human disease caused by an abnormal protein, and sickle cell anemia became the first disease understood at the molecular level. Using electrophoresis, they demonstrated that individuals with sickle cell disease had a modified form of hemoglobin in their red blood cells, and that individuals with sickle cell trait had both the normal and abnormal forms of hemoglobin. This was also the first demonstration that Mendelian inheritance determined the specific physical properties of proteins, not simply their presence or absence—the dawn of molecular genetics.

Molecular medicine and medical research

In 1941, at age 40, Pauling was diagnosed with Bright's disease, a renal disease. Experts believed then that Bright's disease was untreatable. With the help of Dr. Thomas Addis at Stanford, Pauling was able to control the disease with Addis' then unusual, low protein, salt-free diet. Addis also prescribed vitamins and minerals for all his patients.

In 1951, Pauling gave a lecture entitled, "Molecular Medicine".[54] In the late 1950s, Pauling worked on the role of enzymes in brain function, believing that mental illness may be partly caused by enzyme disfunction. It wasn't until he read "Niacin Therapy in Psychiatry" by Abram Hoffer in 1965 that he realized that vitamins might have important biochemical effects unrelated to their prevention of associated deficiency diseases. Pauling published a brief paper, "Orthomolecular psychiatry", in the journal Science in 1968 (PMID 5641253) that gave name and principle to the
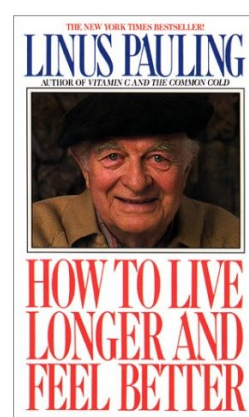
popular but controversial megavitamin therapy movement of the 1970s. Pauling coined the term "orthomolecular" to refer to the practice of varying the concentration of substances normally present in the body to prevent and treat disease. His ideas formed the basis of orthomolecular medicine, which is not generally practiced by conventional medical professionals and is strongly criticized by some.[55] [56]

Pauling's work on vitamin C in his later years generated much controversy. He was first introduced to the concept of high-dose vitamin C by biochemist Irwin Stone in 1966. After becoming convinced of its worth, Pauling took 3 grams of vitamin C every day to prevent colds (Dunitz 1996:333). Excited by the results, he researched the clinical literature and published *Vitamin C and the Common Cold* in 1970. He began a long clinical collaboration with the British cancer surgeon Ewan Cameron in 1971 on the use of intravenous and oral vitamin C as cancer therapy for terminal patients.[57] Cameron and Pauling wrote many technical papers and a popular book, "Cancer and Vitamin C", that discussed their observations. Pauling made vitamin C popular with the public, but the medical establishment regarded his claims that vitamin C could prevent colds and cure cancer as quackery (Dunitz 1996:333), and considered the case closed after two randomized trials conducted by the Mayo Clinic and published in the *New England Journal of Medicine* failed to replicate[58] Pauling's study, which found that vitamin C supplementation lengthened survival times significantly.[59] Pauling denounced the conclusions of these studies and handling of the final study as "fraud and deliberate misrepresentation."[60] [61] Pauling's original study, based on the observational studies of intravenous vitamin C by McCormick and Klenner, used intravenous vitamin C for the first ten days, but the randomized trials did not.[58] Pauling published critiques of the second Mayo-Moertel cancer trial's flaws over several years as he was able to slowly unearth some of the trial's undisclosed details.[62] However, the wave of adverse publicity generated by Moertel and the media effectively undercut Pauling's credibility and his vitamin C work for a generation,[63] and the oncological mainstream continued with other avenues of treatment.[64] Always precariously perched since his molecular biologically inspired crusade to stop atmospheric nuclear testing in the 1950s,[65] the 1985 Mayo-Moertel confrontation left Pauling isolated from his institutional funding sources, academic support and a bemused public. However, Pauling did have allies in his cause to promote vitamin C. He worked with The Institutes for the Achievement of Human Potential, an organization that treats brain-injured children, to advocate the use of the vitamin."[66] He later collaborated with the Canadian physician Abram Hoffer on a micronutrient regimen, including high-dose vitamin C, as adjunctive cancer therapy.[67] Of late the "connection between vitamin C and cancer has become a respectable topic", and it was the subject of a Washington DC NIH conference in 1990 (Dunitz 1996:334).

As of 2007, new evidence was proposed by a Canadian group showing that intravenous vitamin C can achieve plasma concentrations up to 70-fold higher than oral vitamin C.[68] The selective toxicity of vitamin C for cancer cells has been demonstrated in-vitro (i.e., in a cell culture Petri dish), and was reported in 2005.[69] The combination of case-report data and preclinical information suggest biological plausibility and the possibility of clinical efficacy at the possible expense of critical toxicity at active doses; future clinical testing will ultimately determine the utility and safety of intravenous high-dose vitamin C treatments for patients with cancer. Though limited in scope, researchers also observed longer-than expected survival times in three patients treated with high doses of intravenous vitamin C.[70] The researchers are reportedly planning a new Phase I clinical trial.[71]

Linus Pauling's book *How to Live Longer and Feel Better*, advocated very high intake of vitamins.

With two colleagues, Pauling founded the Institute of Orthomolecular Medicine in Menlo Park, California, in 1973, which was soon renamed

the Linus Pauling Institute of Science and Medicine. Pauling directed research on vitamin C, but also continued his theoretical work in chemistry and physics until his death. In his last years, he became especially interested in the

possible role of vitamin C in preventing atherosclerosis and published three case reports on the use of lysine and vitamin C to relieve angina pectoris. In 1996, the Linus Pauling Institute moved from Palo Alto, California, to Corvallis, Oregon, to become part of Oregon State University, where it continues to conduct research on micronutrients, phytochemicals (chemicals from plants), and other constituents of the diet in preventing and treating disease. Several of the employees that had previously worked at the Linus Pauling Institute in Palo Alto moved on to form the Genetic Information Research Institute.

Nature of the chemical bond

In the late 1920s Pauling began publishing papers on the nature of the chemical bond, leading to his famous textbook on the subject published in 1939. It is based primarily on his work in this area that he received the Nobel Prize in Chemistry in 1954 "for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances". Pauling summarized his work on the chemical bond in *The Nature of the Chemical Bond*, one of the most influential chemistry books ever published.[72] In the 30 years after its first edition was published in 1939, the book was cited more than 16,000 times. Even today, many modern scientific papers and articles in important journals cite this work, more than half a century after first publication.

Part of Pauling's work on the nature of the chemical bond led to his introduction of the concept of orbital hybridization.[73] While it is normal to think of the electrons in an atom as being described by orbitals of types such as *s* and *p*, it turns out that in describing the bonding in molecules, it is better to construct functions that partake of some of the properties of each. Thus the one 2s and three 2p orbitals in a carbon atom can be combined to make four equivalent orbitals (called sp³ hybrid orbitals), which would be the appropriate orbitals to describe carbon compounds such as methane, or the 2s orbital may be combined with two of the 2p orbitals to make three equivalent orbitals (called sp² hybrid orbitals), with the remaining 2p orbital unhybridized, which would be the appropriate orbitals to describe certain unsaturated carbon compounds such as ethylene. Other hybridization schemes are also found in other types of molecules.

Another area which he explored was the relationship between ionic bonding, where electrons are transferred between atoms, and covalent bonding where electrons are shared between atoms on an equal basis. Pauling showed that these were merely extremes, between which most actual cases of bonding fall. It was here especially that Pauling's *electronegativity* concept was particularly useful; the electronegativity difference between a pair of atoms will be the surest predictor of the degree of ionicity of the bond.[74]

The third of the topics that Pauling attacked under the overall heading of "the nature of the chemical bond" was the accounting of the structure of aromatic hydrocarbons, particularly the prototype, benzene.[75] The best description of benzene had been made by the German chemist Friedrich Kekulé. He had treated it as a rapid interconversion between two structures, each with alternating single and double bonds, but with the double bonds of one structure in the locations where the single bonds were in the other. Pauling showed that a proper description based on quantum mechanics was an intermediate structure which was a blend of each. The structure was a superposition of structures rather than a rapid interconversion between them. The name "resonance" was later applied to this phenomenon.[76] In a sense, this phenomenon resembles that of hybridization, described earlier, because it involves combining more than one electronic structure to achieve an intermediate result.

Structure of the atomic nucleus

On September 16, 1952, Pauling opened a new research notebook with these words "*I have decided to attack the problem of the structure of nuclei.*"[77] On October 15, 1965, Pauling published his Close-Packed Spheron Model of the atomic nucleus in two well respected journals, *Science*, and *Proc. Natl. Acad. Sci.*.[78] For nearly three decades, until his death in 1994, Pauling published numerous papers on his spheron cluster model.[79] [80] [81] [82] [83] [84]

Few modern text books on nuclear physics discuss the Pauling Spheron Model of the Atomic Nucleus, yet it provides a unique perspective, well published in the leading journals of science, on how fundamental "clusters of nucleons" can form shell structure in agreement with recognized theory of quantum mechanics. Pauling was well versed in quantum mechanics; he co-authored one of the first textbooks on the subject, *Introduction to Quantum Mechanics with Applications to Chemistry*. In a 2006 review of models of atomic nuclei, Norman D. Cook said of the Pauling Spheron Model: *"...the model leads to a rather common-sense molecular build-up of nuclei and has an internal logic that is hard to deny...however, despite two decades of advocacy by Pauling, nuclear theorists have not elaborated on the idea of nucleon spherons, and Pauling's model has not entered mainstream nuclear theory."*[85] Taken at face value, the conclusions of Norman Cook imply that the 1965 Pauling Spheron Model of the atomic nucleus has simply been ignored.

The Pauling spheron nucleon clusters include the deuteron[NP], helion [PNP], and triton [NPN]. Even-even nuclei were described as being composed of clusters of alpha particles, as has often been done for light nuclei. He made an effort to derive the shell structure of nuclei from the Platonic solids rather than starting from an independent particle model as in the usual shell model. It was sometimes said at that time that this work received more attention than it would have if it had been done by a less famous person, but more likely Pauling was taking a unique approach to understanding the relatively new discovery in the late 1940s of Maria Goeppert-Mayer of structure within the nucleus. In an interview given in 1990 Pauling commented on his model:[86]

> Now recently, I have been trying to determine detailed structures of atomic nuclei by analyzing the ground state and excited state vibrational bends, as observed experimentally. From reading the physics literature, Physical Review Letters and other journals, I know that many physicists are interested in atomic nuclei, but none of them, so far as I have been able to discover, has been attacking the problem in the same way that I attack it. So I just move along at my own speed, making calculations...

Legacy

Pauling died of prostate cancer on August 19, 1994, at 7:20 PM at home in Big Sur, California. He was 93 years old.[87] [88] A grave marker for him is in Oswego Pioneer Cemetery in Lake Oswego, Oregon.[88] [89]

Pauling was included in a list of the 20 greatest scientists of all time by the magazine New Scientist, with Albert Einstein being the only other scientist from the twentieth century on the list. Gautam R. Desiraju, the author of the Millennium Essay in Nature,[90] claimed that Pauling was one of the greatest thinkers and visionaries of the millennium, along with Galileo, Newton, and Einstein. Pauling is notable for the diversity of his interests: quantum mechanics, inorganic chemistry, organic chemistry, protein structure, molecular biology, and medicine. In all these fields, and especially on the boundaries between them, he made decisive contributions. His work on chemical bonding marks the beginning of modern quantum chemistry, and many of his contributions like hybridization and electronegativity have become part of standard chemistry textbooks. His valence bond approach fell short of accounting quantitatively for some of the characteristics of molecules, such as the paramagnetic nature of oxygen and the color of organometallic complexes, and would later be superseded by the Molecular Orbital Theory of Robert Mulliken. However, the Valence Bond theory still exists in its modern form and competes with the Molecular Orbital Theory and Density Functional Theory (DFT) for describing the chemical phenomena.[91] Pauling's work on crystal structure contributed significantly to the prediction and elucidation of the structures of complex minerals and compounds. His discovery of the alpha helix and beta sheet is a fundamental foundation for the study of protein structure.

Francis Crick acknowledged Pauling as the "father of molecular biology". His discovery of sickle cell anemia as a "molecular disease" opened the way toward examining genetically acquired mutations at a molecular level.

Pauling's work on the molecular basis of disease and its treatment is being carried on by a number of researchers, notably those at the Linus Pauling Institute, which lists a dozen principal investigators and faculty who study the role of micronutrients and phytochemicals in health and disease.

Items named after Pauling include "Pauling" street located in Foothill Ranch, California (notably once home to vitamin C/Emergen-C maker Alacer Corp. Founder Jay Patrick was a friend of Linus Pauling.), Linus Pauling Drive in Hercules, California, Linus and Eva Helen Pauling Hall at Soka University of America in Aliso Viejo, California, Linus Pauling Middle School in Corvallis, Oregon, and Pauling Field a small airfield located in Condon, Oregon. Dr. Pauling spent his youth in Condon. Additionally, one wing of the Valley Library at Oregon State University bears his name.

Linus Torvalds, developer of the Linux kernel, is named after Pauling.[92]

On March 6, 2008, the United States Postal Service released a 41 cent stamp honoring Pauling.[93] His description reads: "A remarkably versatile scientist, structural chemist Linus Pauling (1901−1994) won the 1954 Nobel Prize in Chemistry for determining the nature of the chemical bond linking atoms into molecules. His work in establishing the field of molecular biology; his studies of hemoglobin led to the classification of sickle cell anemia as a molecular disease." The other scientists on this sheet include Gerty Cori, biochemist, Edwin Hubble, astronomer, and John Bardeen, physicist.

California Governor Arnold Schwarzenegger and First Lady Maria Shriver announced on May 28, 2008 that Pauling would be inducted into the California Hall of Fame, located at The California Museum for History, Women and the Arts. The induction ceremony was scheduled to take place December 15, 2008. Pauling's son was asked to accept the honor in his place.

Pauling appears in the 2006 novel *Visibility* by Boris Starling, who later named his son Linus.

Honors and awards

Pauling received numerous awards and honors during his career. Following are awards and honors he has received.[94]

- 1931 Langmuir Prize, American Chemical Society
- 1941 Nichols Medal, New York Section, American Chemical Society
- 1947 Davy Medal, Royal Society
- 1948 United States Presidential Medal for Merit
- 1952 Pasteur Medal, Biochemical Society of France
- 1954 Nobel Prize in Chemistry
- 1955 Addis Medal, National Nephrosis Foundation
- 1955 Phillips Memorial Award, American College of Physicians
- 1956 Avogadro Medal, Italian Academy of Science
- 1957 Paul Sabatier Medal
- 1957 Pierre Fermat Medal in Mathematics
- 1957 International Grotius Medal
- 1961 Humanist of the Year, American Humanist Association
- 1962 Nobel Peace Prize
- 1965 Republic of Italy
- 1965 Medal, Academy of the Rumanian People's Republic
- 1966 Linus Pauling Medal
- 1966 Silver Medal, Institute of France

- 1966 Supreme Peace Sponsor, World Fellowship of Religion
- 1968 Lenin Peace Prize
- 1972 United States National Medal of Science
- 1972 International Lenin Peace Prize
- 1977 Lomonosov Gold Medal, USSR Academy of Science
- 1979 Medal for Chemical Sciences, National Academy of Science
- 1984 Priestley Medal, American Chemical Society
- 1984 Award for Chemistry, Arthur M. Sackler Foundation
- 1987 Award in Chemical Education, American Chemical Society
- 1989 Vannevar Bush Award, National Science Boardv
- 1990 Richard C. Tolman Medal, Southern California, Section, American Chemical Society
- 2008 "American Scientists" US stamp series, $0.41, for his sickle cell disease work

Publications

- Pauling, L. *The Nature of the Chemical Bond.* Cornell University Press ISBN 0-8014-0333-2
  - Manuscript notes and typescripts (clear images) [95]
- Pauling, L., and Wilson, E. B. *Introduction to Quantum Mechanics with Applications to Chemistry* (Dover Publications) ISBN 0-486-64871-0
- Pauling, L. *Vitamin C, the Common Cold and the Flu* (W.H. Freeman and Company) ISBN 0-7167-0360-2
- Cameron E. and Pauling, L. *Cancer and Vitamin C: A Discussion of the Nature, Causes, Prevention, and Treatment of Cancer With Special Reference to the Value of Vitamin C* (Camino Books) ISBN 0-940159-21-X
- Pauling, L. *How to Live Longer and Feel Better* (Avon Books) ISBN 0-380-70289-4
- Pauling, L. *Linus Pauling On Peace - A Scientist Speaks Out on Humanism and World Survival* (Rising Star Press) ISBN 0-933670-03-6
- Pauling, L. *General Chemistry* (Dover Publications) ISBN 0-486-65622-5
- A Lifelong Quest for Peace with Daisaku Ikeda
- Pauling, L. *The Architecture of Molecules*
- Pauling, L. *No More War!*
- Abram Hoffer and Pauling, L. *Healing Cancer. Complementary Vitamin & Drug Treatments* (CCNM Press Inc.)

See also

- 1920 US Census with Pauling in Portland, Oregon

References

- Dunitz, Jack D. (November 1996). "Linus Carl Pauling, February 28, 1901–August 19, 1994" [96] (– Scholar search [97]). *Biographical Memoirs of Fellows of the Royal Society* **42**: 316–338. doi:10.1098/rsbm.1996.0020 [98].
- Goertzel, Ted; Ben Goertzel (1995). *Linus Pauling: A Life in Science and Politics*. Basic Books. ISBN 0465006728.
- Hager, Thomas (1995). *Force of Nature: The Life of Linus Pauling*. Simon & Schuster. ISBN 0684809095.
- Hager, Thomas (1998). *Linus Pauling and the Chemistry of Life*. Oxford University Press. ISBN 0195139720.
- Marinacci, Barbara; Ramesh Krishnamurthy (1998). *Linus Pauling on Peace*. Rising Star Press. ISBN 0933670036.
- Mead, Clifford; Thomas Hager (eds.) (2001). *Linus Pauling: Scientist and Peacemaker*. Oregon State University Press. ISBN 0870714899.
- Serafini, Anthony (1989). *Linus Pauling: A Man and His Science*. Paragon House. ISBN 155778440X.

Further reading

- Patrick Coffey, Cathedrals of Science: The Personalities and Rivalries That Made Modern Chemistry, Oxford University Press, 2008. ISBN 978-0-19-532134-0

External links

- Linus Pauling Online [99] a Pauling portal created by Oregon State University Libraries
- Francis Crick: The Impact of Linus Pauling on Molecular Biology (transcribed video from the 1995 Oregon State University symposium) [86]
- The Ava Helen and Linus Pauling Papers at the Oregon State University Libraries [100]
- The Pauling Catalogue [101]
- The Pauling Blog [102]
- Linus Pauling (1901−1994) [103]
- National Academy of Sciences biography [104]
- Caltech oral history interview [105]
- Berkeley Conversations With History interview [106]
- Linus Pauling Centenary Exhibit [107]
- Linus Pauling from The Dictionary of Unitarian and Universalist Biography [108]
- Linus Pauling Investigates Vitamin C [109]
- The Linus Pauling Institute [110] at Oregon State University and
- The Many Lives of Linus Pauling: A Review of Reviews J. Chem. Educ. [111]
- Pauling's CV [112]
- Publications of Pauling [113]
- Linus and Ava Helen Pauling Hall [114] at Soka University of America, devoted to pacifism in global citizenship.
- Works by or about Linus Pauling [115] in libraries (WorldCat catalog)

References

[1] http://www.adherents.com/people/100_scientists.html
[2] http://www.biomedresearch.net/linuspauling.htm
[3] Marie Curie, John Bardeen and Frederick Sanger are the others. As Watson attests, Pauling also came close to being the discoverer of DNA's structure for which Francis Crick, James Watson and Maurice Wilkins received the prize.
[4] Dunitz, p. 222.
[5] Hager, p. 22.
[6] Mead and Hager, p. 8.
[7] Goertzel and Goertzel, p. 1.
[8] Goertzel and Goertzel, p. 2.
[9] Hager, p. 21.
[10] Goertzel and Goertzel, p. 6.
[11] Hager, p. 24.
[12] Goertzel and Goertzel, p. 4.
[13] Goertzel and Goertzel, p. 5.
[14] Goertzel and Goertzel, p. 12.
[15] Goertzel and Goertzel, p. 13.
[16] Mead and Hager, p. 9.
[17] Dunitz, p. 223.
[18] Goertzel and Goertzel, p. 17.
[19] Goertzel and Goertzel, p. 21.
[20] Goertzel and Goertzel, p. 22.
[21] Hager, p. 48.
[22] "Linus Pauling − Biography" (http://nobelprize.org/nobel_prizes/peace/laureates/1962/pauling-bio.html). Nobel Foundation. . Retrieved 2007-08-05.
[23] Bourgoin, Suzanne M.; Paula K. Byers (1998). *Encyclopedia of World Biography*. Thomson Gale. Vol. 12, p. 150. ISBN 0787622214.

[24] Goertzel and Goertzel, p. 23..

[25] Goertzel and Goertzel, p. 24.

[26] Goertzel and Goertzel, p. 25.

[27] Goertzel and Goertzel, p. 26.

[28] Swanson, Stephen (2000-10-03). "OSU fraternity to donate Pauling treasures to campus library" (http://oregonstate.edu/dept/ncs/newsarch/2000/Oct00/pauling.htm). Oregon State University. . Retrieved 2008-03-11.

[29] Goertzel and Goertzel, p. 29.

[30] Goertzel and Goertzel, p. 30.

[31] Goertzel and Goertzel, p. 31.

[32] Linus Pauling Institute. "Linus Pauling: A Biographical Timeline" (http://lpi.oregonstate.edu/lpbio/timeline.html). . Retrieved 2007-08-05.

[33] "... I [Pauling] am not, however, militant in my atheism. The great English theoretical physicist Paul Dirac is a militant atheist. I suppose he is interested in arguing about the existence of God. I am not. It was once quipped that there is no God and Dirac is his prophet." Linus Pauling & Daisaku Ikeda (1992). *A Lifelong Quest for Peace: A Dialogue*. Jones & Bartlett. pp. 22. ISBN 0867202777.

[34] Tom Hager (December 2004). ""The Langmuir Prize"" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/bond/narrative/page28.html). Oregon State University Libraries Special Collections. . Retrieved 2008-02-29.

[35] Linus Pauling (March 1932). ""The nature of the chemical bond. III. The transition from one extreme bond type to another."" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/bond/papers/1932p.2.html). Journal of the American Chemical Society. . Retrieved 2008-02-29.

[36] Thomas Hager (1995). *Force of Nature: The Life of Linus Pauling*. Simon & Schuster. ISBN 0684809095., pp. 152

[37] "The Linus Pauling Papers: Biographical Information" (http://profiles.nlm.nih.gov/MM/Views/Exhibit/narrative/biographical.html). United States National Library of Medicine. . Retrieved 2008-02-11.

[38] Paulus, John Allen (1995-11-05). "Pauling's Prizes" (http://query.nytimes.com/gst/fullpage.html?res=9D05E3DE1739F936A35752C1A963958260&). *New York Times*. . Retrieved 2007-12-09.

[39] Thomas Hager (November 29, 2007). "Einstein" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/peace/narrative/page9.html). Oregon State University Libraries Special Collections. . Retrieved 2007-12-13.

[40] "Linus Pauling" (http://www.woodrow.org/teachers/ci/1992/Pauling.html). . Retrieved 2007-12-11. "[In] January of 1952, Pauling requested a passport to attend a meeting in England ... The passport was denied because granting it "would not be in the best interest of the United States." He applied again and wrote President Eisenhower, asking him to arrange the issuance of the passport since, "I am a loyal citizen of the United States. I have never been guilty of any unpatriotic or criminal act.""

[41] Linus Pauling (May 1952). "The Department of State and the Structure of Proteins" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/peace/notes/1952a.18.html). Oregon State University Libraries Special Collections. . Retrieved 2007-12-13.

[42] Thomas Hager (November 29, 2007). "Russell/Einstein" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/peace/narrative/page25.html). Oregon State University Libraries Special Collections. . Retrieved 2007-12-13.

[43] http://beckerexhibits.wustl.edu/mowihsp/bios/reiss.htm/

[44] Louise Zibold Reiss (November 24, 1961). "Strontium-90 Absorption by Deciduous Teeth: Analysis of teeth provides a practicable method of monitoring strontium-90 uptake by human populations" (http://www.sciencemag.org/cgi/reprint/134/3491/1669.pdf). Science. . Retrieved 2009-10-13.

[45] Thomas Hager (November 29, 2007). "Strontium-90" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/peace/narrative/page26.html). Oregon State University Libraries Special Collections. . Retrieved 2007-12-13.

[46] Thomas Hager (November 29, 2007). "The Right to Petition" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/peace/narrative/page27.html). Oregon State University Libraries Special Collections. . Retrieved 2007-12-13.

[47] Linus Pauling; Edward Teller (1958). "Teller vs. Pauling" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/peace/video/1958v.3.html). Oregon State University Libraries Special Collections. . Retrieved 2007-12-13.

[48] Linus Pauling (1963-10-10). "Notes by Linus Pauling. October 10, 1963." (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/peace/notes/rnb23-100.html). Oregon State University Libraries Special Collections. . Retrieved 2007-12-13.

[49] Stephen F Mason (July 1999). "The Science and Humanism of Linus Pauling (1901-1994)." (http://cabierta.uchile.cl/revista/6/linus.htm). Ciencia Abierta. . Retrieved 2009-08-04.

[50] "Linus Pauling's DNA Model" (http://www.farooqhussain.org/projects/paulingdnamodel/document_view). . Retrieved 2007-08-06.

[51] "Pauling biography citing State Department's revocation of Pauling's passport in 1952" (http://www.woodrow.org/teachers/ci/1992/Pauling.html). . Retrieved 2007-12-11.

[52] Hager, Thomas (1995). *Force of Nature: The Life of Linus Pauling*. Simon & Schuster. ISBN 0684809095., pp. 414–415

[53] Pauling, Linus; Harvey Itano, S. J. Singer, Ibert Wells (November 1949). "Sickle Cell Anemia, a Molecular Disease" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/blood/papers/1949p.15.html). Science. . Retrieved 2007-08-05.

[54] Pauling, Linus (October 1951). "Molecular Medicine" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/blood/pictures/1951s.17.html). Ava Helen and Linus Pauling Papers. . Retrieved 2007-08-05.

[55] Cassileth, BR (1998:67). *Alternative Medicine Handbook: the Complete Reference Guide to Alternative and Complementary Therapies*. New York: W.W. Norton & Co..

[56] "Vitamin Therapy, Megadose / Orthomolecular Therapy" (http://www.bccancer.bc.ca/PPI/UnconventionalTherapies/ VitaminTherapyMegadoseOrthomolecularTherapy.htm). BC Cancer Agency. February 2000. . Retrieved 2007-08-05.

[57] Ewan Cameron M.D.. "Cancer bibliography" (http://www.doctoryourself.com/biblio_cameron.html). Doctoryourself.com. . Retrieved 2007-08-05.

[58] Chen Q et al. (2007). Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. (http://www.pnas.org/cgi/content/full/104/21/8749) *Proceedings for the National Academy of Sciences*. See reference to citations 5,6, and 7.

[59] Cameron E, Pauling L (1978) Supplemental Ascorbate in the Supportive Treatment of Cancer: Reevaluation of Prolongation of Survival Times in Terminal Human Cancer (http://www.pnas.org/cgi/content/abstract/75/9/4538)

[60] Ted Goertzel (1996). "Analyzing Pauling's Personality: A Three Generational, Three Decade Project" (http://oregonstate.edu/dept/ Special_Collections/subpages/ahp/1995symposium/goertzel.html). Special Collections, Oregon State University Libraries. . Retrieved 2007-08-05.

[61] (2005) (http://www.press.uchicago.edu/Misc/Chicago/113663.html), University of Chicago Press, ISBN 0-226-11366-3, Excerpt from pages 89–111

[62] Mark Levine; Sebastian J. Padayatty, Hugh D. Riordan, Stephen M. Hewitt, Arie Katz, L. John Hoffer (2006-03-28). "Intravenously administered vitamin C as cancer therapy: three cases" (http://www.cmaj.ca/cgi/content/full/174/7/937#T217). CMA Media. . Retrieved 2007-08-05.

[63] "Intravenous Vitamin C Kills Cancer Cells" (http://www.knowledgeofhealth.com/report.asp?story=Intravenous Vitamin C Kills Cancer Cells). Proc. Natl. Acad. Sci.. 2005-09-12. . Retrieved 2007-08-05.

[64] Collin, Harry; Pinch, Trevor (2007). *Dr. Golem: How to Think about Medicine*. Chicago: University of Chicago Press. ISBN 0226113671.

[65] "No More War!" (http://web.archive.org/web/20060907091808/http://www.paulingexhibit.org/bio/sec_09.html). Linus Pauling and the Twentieth Century. Archived from the original (http://www.paulingexhibit.org/bio/sec_09.html) on 2007-08-06. . Retrieved 2007-08-06.

[66] Pauling, Linus (November 1978). Ralph Pelligra, ed.. ed. "Orthomolecular enhancement of human development" (http://profiles.nlm.nih. gov/MM/B/B/K/G/_/mmbbkg.pdf) (PDF). *Human Neurological Development: Past, Present, and Future. A Joint Symposium Sponsored by NASA/Ames Research Center and the Institutes for the Achievement of Human Potential. NASA CP 2063*: 47–51. .

[67] Andrew W. Saul; Dr. Abram Hoffer. "Abram Hoffer, M.D., Ph.D. 50 Years of Megavitamin Research, Practice and Publication" (http:// www.doctoryourself.com/biblio_hoffer.html). Doctoryourself.com. . Retrieved 2007-08-05.

[68] Sebastian et al. *Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use* (full-text (http://www.annals.org/cgi/content/ full/140/7/533)). *Annals of Internal Medicine*.

[69] Chen Q, Espey M, Krishna M, Mitchell J, Corpe C, Buettner G, Shacter E, Levine M (2005). "Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues" (http://www.pubmedcentral.nih.gov/articlerender. fcgi?tool=pmcentrez&artid=1224653). *Proc Natl Acad Sci USA* **102** (38): 13604–9. doi: 10.1073/pnas.0506390102 (http://dx.doi.org/10. 1073/pnas.0506390102). PMID 16157892 (http://www.ncbi.nlm.nih.gov/pubmed/16157892).

[70] Padayatty S, Riordan H, Hewitt S, Katz A, Hoffer L, Levine M (2006). "Intravenously administered vitamin C as cancer therapy: three cases" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1405876). *CMAJ* **174** (7): 937–42. doi: 10.1503/cmaj.050346 (http://dx.doi.org/10.1503/cmaj.050346). PMID 16567755 (http://www.ncbi.nlm.nih.gov/pubmed/16567755).

[71] Assouline S, Miller W (2006). "High-dose vitamin C therapy: renewed hope or false promise?" (http://www.pubmedcentral.nih.gov/ articlerender.fcgi?tool=pmcentrez&artid=1405871). *CMAJ* **174** (7): 956–7. doi: 10.1503/cmaj.060228 (http://dx.doi.org/10.1503/cmaj. 060228). PMID 16567756 (http://www.ncbi.nlm.nih.gov/pubmed/16567756).

[72] Thomas Hager (December 2004). "The Nature of the Chemical Bond" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/ bond/narrative/page46.html). Oregon State University Libraries Special Collections. . Retrieved 2008-02-29.

[73] Linus Pauling (1928). ""London's paper. General ideas on bonds."" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/ bond/notes/sci3.001.21.html). Oregon State University Libraries Special Collections. . Retrieved 2008-02-29.

[74] Linus Pauling (1930s). ""Notes and Calculations re: Electronegativity and the Electronegativity Scale"" (http://osulibrary.oregonstate.edu/ specialcollections/coll/pauling/bond/notes/sci5.001.14.html). Oregon State University Libraries Special Collections. . Retrieved 2008-02-29.

[75] Linus Pauling (1934-01-06). ""Benzene"" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/bond/notes/sci2.004.6. html). Oregon State University Libraries Special Collections. . Retrieved 2008-02-29.

[76] Linus Pauling (1946-07-29). ""Resonance"" (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/bond/notes/1946a.3. html). Oregon State University Libraries Special Collections. . Retrieved 2008-02-29.

[77] Oregon State Special Collections (http://osulibrary.oregonstate.edu/specialcollections/rnb/27/27-124.html)

[78] Pauling, Linus (October 1965). "The close-packed-spheron theory and nuclear fission" (http://osulibrary.orst.edu/specialcollections/rnb/ 26/26-026.html). Science. . Retrieved 2007-08-05.

[79] Pauling, Linus (October 1965). "The close-packed spheron model of atomic nuclei and its relation to the shell model" (http://osulibrary. orst.edu/specialcollections/rnb/26/26-012.html). Science. . Retrieved 2007-08-05.

[80] Pauling, Linus (July 1966). "The close-packed-spheron theory of nuclear structure and the neutron excess for stable nuclei (Dedicated to the seventieth anniversary of Professor [[Horia Hulubei (http://osulibrary.orst.edu/specialcollections/rnb/26/26-048.html)])". Science. . Retrieved 2007-08-05.

[81] Pauling, Linus (December 1967). "Magnetic-moment evidence for the polyspheron structure of the lighter atomic nuclei" (http://osulibrary. orst.edu/specialcollections/rnb/26/26-068.html). Science. . Retrieved 2007-08-05.

[82] Pauling, Linus (November 1969). "Orbiting clusters in atomic nuclei" (http://osulibrary.orst.edu/specialcollections/rnb/26/26-075. html). Science. . Retrieved 2007-08-05.

[83] Pauling, Linus; Arthur B. Robinson (1975). "Rotating clusters in nuclei" (http://osulibrary.orst.edu/specialcollections/rnb/26/26-084. html). Canadian Journal of Physics. . Retrieved 2007-08-05.

[84] Pauling, Linus (1991). "Transition from one revolving cluster to two revolving clusters in the ground-state rotational bands of nuclei in the lanthanon region" (http://osulibrary.orst.edu/specialcollections/rnb/26/26-125.html). *Proc. Natl. Acad. Sci.* **88 month=February**. . Retrieved 2007-08-05.

[85] Norman D. Cook, Models of the Atomic Nucleus, 2006, Springer, p. 71.

[86] Linus Pauling Interview - page 9 / 9 - Academy of Achievement (http://www.achievement.org/autodoc/page/pau0int-9)

[87] Goertzel and Goertzel, p. 247.

[88] Linus Pauling dies at 93. *The Oregonian*, August 20, 1994.

[89] Linus C. Pauling. (http://www.findagrave.com/cgi-bin/fg.cgi?page=gr&GSln=pauling&GSfn=linus&GSbyrel=all&GSdy=1994& GSdyrel=in&GSob=n&GRid=22440&) Find A Grave. Retrieved December 4, 2007.

[90] Desiraju, G.R. (2000-11-23). "The all-chemist" (http://www.nature.com/nature/journal/v408/n6811/pdf/408407A0.pdf) (PDF). Nature. . Retrieved 2007-08-05.

[91] "A Conversation on VB vs MO Theory: A Never-Ending Rivalry?" (http://pubs3.acs.org/acs/journals/doilookup?in_doi=10.1021/ ar030162a). ACS Publications. 2003. pp. 750–756. . Retrieved 2007-08-05.

[92] Moody, Glyn (2002). *Rebel Code: Linux and the Open Source Revolution* (http://www.perseusbooksgroup.com/perseus/ book_detail_redirect.do?imprintCid=BA&isbn=0738206709). Perseus Books Group. pp. 336. ISBN 0738206709. .

[93] Odegard, Kyle (2008-03-07). "Linus Pauling stamp debuts at university" (http://www.gtconnect.com/articles/2008/03/07/news/ community/3aaa03_pauling.txt). *Gazette-Times*. .

[94] Jeffrey L. Sturchio (April 1987). "Linus C. Pauling - Honors" (http://www.chemheritage.org/exhibits/ex-oral-detail.asp?ID=67& Numb=1#honors). Chemical Heritage Foundation. . Retrieved 2010-01-09.

[95] http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/bond/index.html

[96] http://www.jstor.org/view/00804606/ap030044/03a00200/0

[97] http://scholar.google.co.uk/scholar?hl=en&lr=&q=author%3ADunitz+intitle%3ALinus+Carl+Pauling%2C+28+February+ 1901%E2%80%9319+August+1994&as_publication=Biographical+Memoirs+of+Fellows+of+the+Royal+Society&as_ylo=1996& as_yhi=1996&btnG=Search

[98] http://dx.doi.org/10.1098%2Frsbm.1996.0020

[99] http://pauling.library.oregonstate.edu

[100] http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/index.html

[101] http://paulingcatalogue.org

[102] http://paulingblog.wordpress.com

[103] http://www.users.muohio.edu/shermalw/honors_2001_fall/honors_papers_2001/Lowrey_LPauling.htm

[104] http://www.nap.edu/readingroom/books/biomems/lpauling.html

[105] http://oralhistories.library.caltech.edu/archive/00000018/00/OH_Pauling_L.pdf

[106] http://globetrotter.berkeley.edu/conversations/Pauling

[107] http://pauling.library.oregonstate.edu/exhibit/

[108] http://www25.uua.org/uuhs/duub/articles/linuspauling.html

[109] http://www.alternativehealth.co.nz/vitaminc/paulinginvestigates.htm

[110] http://lpi.oregonstate.edu/

[111] http://jchemed.chem.wisc.edu/Journal/Issues/1996/Sep/absA210.html

[112] http://www.chemheritage.org/exhibits/ex-oral-detail.asp?ID=67&Numb=1

[113] http://charon.girinst.org/~zeke/test.bit.pdf

[114] http://www.soka.edu/page.cfm?p=206

[115] http://worldcat.org/identities/lccn-n79-144786

Johnjoe McFadden

Johnjoe McFadden	
Born	17 May 1956 Donegal, Ireland
Residence	🇬🇧 UK
Ethnicity	🇮🇪 Irish
Fields	Biologist
Institutions	University of Surrey St Mary's Hospital Medical School St George's, University of London
Alma mater	Imperial College London
Doctoral advisor	Ken Buck
Known for	Diagnosis of meningitis

Johnjoe McFadden (born 17 May 1956 in Donegal, Ireland) is an Irish / British scientist, academic and writer. He is Professor of Molecular Genetics at the University of Surrey, United Kingdom.

Life

He was born in Donegal, Ireland but raised in the UK. He has joint British/Irish Nationality.

He obtained his BSc in Biochemistry University of London in 1977 and his PhD at Imperial College London in 1982. He went on to work on human genetic diseases and then infectious diseases, at St Mary's Hospital Medical School, London (1982-84) and St George's Hospital Medical School, London (1984-88) and then at the University of Surrey in Guildford, UK.

For more than a decade, McFadden has specialised in examining the genetics of microbes such as the agents of tuberculosis and meningitis and invented a test for the diagnosis of meningitis.

He has published more than 100 articles in scientific journals on subjects as wide-ranging as bacterial genetics, tuberculosis, idiopathic diseases and computer modelling of evolution. He has contributed to more than a dozen books and has edited a book on the genetics of mycobacteria.

He produced a widely reported artificial life computer model which modelled evolution in organisms.

He has lectured extensively in the UK, Europe, the USA and Japan and his work has been featured in radio, television and national newspaper articles particularly for the Guardian. His present post, which he has held since 2001, is Professor of Molecular Genetics at the University of Surrey.

Living in London, he is married and has one son.

Writing

McFadden wrote the popular science book, *Quantum Evolution* (see wikipedia article Quantum evolution (alternative) for details of this concept), published in the UK by HarperCollins in 2001, in the US by Norton in 2002 and currently being translated for publication by Kyoritsu Shuppan in Japan in 2003. The book examines the role of quantum mechanics in life, evolution and consciousness.

McFadden regularly writes articles for The Guardian newspaper in the UK, on topics as varied as quantum mechanics, evolution and genetically modified crops, and has reviewed books there. The Washington Post and Frankfurter Allgemeine Sonntagszeitung have also published articles written by him.

See also

- Quantum Aspects of Life

References

- Johnjoe Mcfadden's Homepage [1] at Surrey University
- Johnjoe McFadden's *Machines Like Us* interview [2]
- School of Biomedical and Molecular Sciences at University of Surrey [3] Professor Johnjoe McFadden
- Curriculum Vitae [4]
- Quantum Evolution [5] - Explore the role of quantum mechanics in life, evolution and consciousness (includes excerpts from the book, Quantum Evolution.)

References

[1] http://www.surrey.ac.uk/qe/
[2] http://www.machineslikeus.com/cms/MLU-interviews-johnjoe-mcfadden.html
[3] http://www.surrey.ac.uk/SBMS/ACADEMICS_homepage/mcfadden_johnjoe/
[4] http://www.surrey.ac.uk/SBMS/ACADEMICS_homepage/mcfadden_johnjoe/pdfs/McFadden%20cv.pdf
[5] http://www.surrey.ac.uk/qe/quantumevolution.htm

Notable physicists with interests in Biology

William Lawrence Bragg

William Lawrence Bragg	
 William L. Bragg in 1915	
Born	31 March 1890 North Adelaide, South Australia
Died	1 July 1971 (aged 81) Waldringfield, Ipswich, Suffolk, England
Nationality	United Kingdom
Institutions	University of Manchester University of Cambridge
Alma mater	University of Adelaide University of Cambridge
Doctoral advisor	J. J. Thomson W.H. Bragg
Doctoral students	John Crank Ronald Wilfried Gurney
Known for	X-ray diffraction Bragg's Law
Notable awards	Nobel Prize in Physics (1915)
Notes At 25, the youngest person ever to receive a Nobel Prize. He was the son of W.H. Bragg. Note that the PhD did not exist at Cambridge until 1919, and so J. J. Thomson and W.H. Bragg were his equivalent mentors.	

Sir William Lawrence Bragg, CH, OBE, MC, FRS (31 March 1890 – 1 July 1971) was an English physicist who shared the Nobel Prize in Physics in 1915 with his father Sir William Henry Bragg. He is, to date, the youngest Nobel laureate. He was the director of the Cavendish Laboratory, Cambridge when the epochal discovery of the structure of DNA was made by James D. Watson and Francis Crick in February 1953.

Biography

Early years

Bragg was born in North Adelaide, South Australia. He was an impressionable boy and showed an early interest in science and mathematics. His father, William Henry Bragg, was Elder Professor of Mathematics and Physics at the University of Adelaide. Shortly after starting school aged 5, William Lawrence Bragg fell from his tricycle and broke his arm. His father, who had read about Röntgen's experiments in Europe and was performing his own experiments, used the newly discovered X-rays and his experimental equipment to examine the broken arm. This is the first recorded surgical use of X-rays in Australia.

Bragg was a very able student. After beginning his studies at St Peter's College, in 1904 he went to the University of Adelaide at age 14 to study mathematics, chemistry and physics, graduating in 1908. In the same year his father accepted the Cavendish chair of physics at the University of Leeds, and brought the family back to England. Bragg entered Trinity College, Cambridge in the autumn of 1909 and received a major scholarship in mathematics, despite taking the exam while in bed with pneumonia. After initially excelling in mathematics, he transferred to the physics course in the later years of his studies, and graduated in 1911.

Career

Work on X-ray crystallography

Bragg is most famous for his law on the diffraction of X-rays by crystals. Bragg's law makes it possible to calculate the positions of the atoms within a crystal from the way in which an X-ray beam is diffracted by the crystal lattice. He made this discovery in 1912, during his first year as a research student in Cambridge. He discussed his ideas with his father, who developed the X-ray spectrometer in Leeds. This tool allowed many different types of crystals to be analyzed. The collaboration between father and son led many people to believe that the father had initiated the research, a fact that upset the son.

Work on sound ranging

Bragg's research work was interrupted by both World War I and World War II. During both wars he worked on sound ranging methods for locating enemy guns, in this work he was aided by William Sansome Tucker, Harold Roper Robinson and Henry Harold Hemming. For his work during WWI he was awarded the Military Cross (London Gazette, 1 January 1918) and appointed an Officer of the British Empire (London Gazette, 15 March 1918). He was also mentioned in dispatches on 16 June 1916, 4 January 1917 and 7 July 1919.[1]

In autumn 1915 his brother was killed at Gallipoli. At about the same time, William Lawrence Bragg received the news that he received the Nobel Prize in Physics, aged 25, making him the youngest ever winner of a Nobel Prize.

Between the wars, from 1919 to 1937, he worked at the Victoria University of Manchester as Langworthy Professor of Physics.

After World War II, he returned to Cambridge, splitting the Cavendish Laboratory into research groups. He believed that "the ideal research unit is one of six to twelve scientists and a few assistants".

Work on proteins

In 1948 he became interested in the structure of proteins and was partly responsible for creating a group that used physics to solve biological problems. He played a major part in the 1953 discovery of the structure of DNA, in that he provided support to Francis Crick and James D. Watson who worked under his aegis at the Cavendish.

Bragg's original announcement of the discovery of the structure of DNA was made at a Solvay conference on proteins in Belgium on 8 April 1953 but went unreported by the press, he then gave a talk at Guys Hospital Medical School in London on Thursday, May 14, 1953 which resulted in an article by Ritchie Calder in The News Chronicle of London, on Friday, May 15, 1953, entitled "Why You Are You. Nearer Secret of Life."

Bragg was gratified to see that the X-ray method that he developed forty years before was at the heart of this profound insight into the nature of life itself. At the same time at the Cavendish Max Perutz was also doing his Nobel Prize winning work on the structure of hemoglobin. Bragg subsequently successfully lobbied for and nominated Crick, Watson and Maurice Wilkins for the 1962 Nobel Prize in Physiology or Medicine; Wilkins' share recognized the contribution made by researchers (using X-ray crystallography) at King's College London to the determination of the structure of DNA. Among those researchers was Rosalind Franklin, whose "Photograph 51" showed that DNA was a double helix, not a triple helix as Linus Pauling had proposed. Franklin died before the prize (which only goes to living people) was awarded.

Personal life

He married Alice Hopkinson in 1921. They had four children, Stephen Lawrence, David William, Margaret Alice and Patience Mary. He died at a hospital near his home at Waldringfield, Ipswich, Suffolk.

William Lawrence Bragg's hobbies included painting, literature and a life-long interest in gardening. When he moved to London, he missed having a garden and so worked as a part-time gardener, unrecognised by his employer, until a guest at the house expressed surprise at seeing him there.

Honours and awards

He was knighted by King George VI in 1941[2] and received both the Copley Medal and the Royal Medal of the Royal Society. In 1967 was made a Companion of Honour by the Queen Elizabeth II.

Since 1992 the Australian Institute of Physics has awarded the Bragg Gold Medal for Excellence in Physics [3] to commemorate Sir Lawrence Bragg (in front on the medal) and his father Sir William Bragg for the best PhD thesis by a student at an Australian university.

- Nobel Prize (1915)
- Matteucci Medal (1915)
- Hughes Medal (1931)
- Royal Medal (1946)
- Copley Medal (1966)

Quotations

"The gift of expression is important to them as scientists; the best research is wasted when it is extremely difficult to discover what it is all about … It is even more important when scientists are called upon to play their part in the world of affairs, as is happening to an increasing extent."[4]

Books containing references to Sir Lawrence Bragg

- Biography: Hunter, Graeme. *Light Is A Messenger, the Life and Science of William Lawrence Bragg*, ISBN 0-19-852921-X; Oxford University Press, 2004.
- John Finch; 'A Nobel Fellow On Every Floor', Medical Research Council 2008, 381 pp, ISBN 978-1840469-40-0; this book is all about the MRC Laboratory of Molecular Biology, Cambridge.
- Ridley, Matt; *Francis Cr* ick: Discoverer of the Genetic Code (Eminent Lives)*, first published in July 2006 in the USA and then in the UK. September 2006, by HarperCollins Publishers; 192 pp, ISBN 0-06-082333-X; [This short book is in the publisher's "Eminent Lives" series.]
- John Jenkin: "William and Lawrence Bragg, Father and Son: The Most Extraordinary Collaboration in Science", Oxford University Press, 2008.

See also

- 'Death' of DNA Helix (crystalline) joke funeral card.
- Tactical Artillery Terms from World War I

External links

- [13] First press stories on DNA
- Nobelprize.org - The Nobel Prize for Physics in 1915 [5]
- Nobel Biography [6]
- A collection [7] of digitized materials related to Bragg's and Linus Pauling's structural chemistry research.
- Key Participants: Sir William Lawrence Bragg [8] - *Linus Pauling and the Race for DNA: A Documentary History*
- NOVA Episode on Photograph 51 [146]
- Oral History interview transcript with William Lawrence Bragg 20 June 1969, American Institute of Physics, Niels Bohr Library and Archives [9]

References

[1]   William Van der Kloot, Lawrence Bragg's role in the development of sound-ranging in World War I (http://rsnr.royalsocietypublishing.org/content/59/3/273.full), Notes and Records of the Royal Society, 22 September 2005, vol. 59, no. 3, pp. 273-284.

[2]   [http://www.gazettes-online.co.uk/ViewPDF.aspx? London Gazette January 1941 (http://www.london-gazette.co.uk/issues/35029/supplements/1)

[3]   http://www.aip.org.au/content/bragg

[4]   Gowers, E., *The Complete Plain Words*, Godine, 1988. ISBN 1-56792-203-1.

[5]   http://nobelprize.org/nobel_prizes/physics/laureates/1915/index.html

[6]   http://nobelprize.org/nobel_prizes/physics/laureates/1915/wl-bragg-bio.html

[7]   http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/bond/people/bragg.html

[8]   http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/people/bragg.html

[9]   http://www.aip.org/history/ohilist/28531.html

Nevill Francis Mott

Nevill Francis Mott	
Born	30 September 1905 Leeds, England
Died	8 August 1996 (aged 90) Milton Keynes, Buckinghamshire, England
Nationality	United Kingdom
Fields	Physics
Institutions	University of Manchester Gonville and Caius College, Cambridge University of Bristol
Alma mater	St John's College, Cambridge
Notable awards	Nobel Prize in Physics (1977)

Sir Nevill Francis Mott, CH, FRS (30 September 1905 – 8 August 1996) was an English physicist. He won the Nobel Prize for Physics in 1977 for his work on the electronic structure of magnetic and disordered systems. The award was shared with Philip W. Anderson and J. H. Van Vleck, who had pursued independent research.

Biography

Early years

Mott was born in Leeds to Lilian Mary Reynolds and Charles Francis Mott. and grew up first in the village of Giggleswick, in the West Riding of Yorkshire, where his father was Senior Science Master at the local school. It was a generally secular childhood. The family moved (due to his father's jobs) first to Staffordshire, then to Chester and finally Liverpool, where his father had been appointed Director of Education. Mott was at first educated at home by his mother, who was a Cambridge Mathematics Tripos graduate. His parents had actually met in the Cavendish Laboratory, when both engaged in Physics research. At ten years of age he began formal education at Clifton College in Bristol, then at St. John's College, Cambridge.

Career

Mott was appointed to a lecturership at Manchester University in 1929. He returned to Cambridge in 1930 as a Fellow and lecturer of Gonville and Caius College and in 1933 moved to Bristol University as Melville Wills Professor in Theoretical Physics.

In 1948 he became Henry Overton Wills Professor of Physics and Director of the Henry Herbert Wills Physical Laboratory at Bristol. In 1954 he was appointed Cavendish Professor of Physics at Cambridge, a post he held until 1971. Additionally he served as Master of Gonville and Caius College, 1959-1966.

Mott's accomplishments include explaining theoretically the effect of light on a photographic emulsion (see latent image) and outlining the transition of substances from metallic to nonmetallic states (Mott transition). The term Mott insulator is also named for him.

Mott was elected a Fellow of the Royal Society in 1936. Mott served as president of the Physical Society in 1957. In the early 1960s he was chairman of the British Pugwash group. He was knighted in 1962.[1] He continued to work until he was about ninety. He was made a Companion of Honour in 1995.

Personal life

Mott was married to Ruth Eleanor Horder, and had two daughters, Elizabeth and Alice. He died in Milton Keynes in Buckinghamshire.

Bibliography

- N. F. Mott, *Metal-Insulator Transitions*, second edition (Taylor & Francis, London, 1990). ISBN 0850667836, ISBN 978-0850667837
- N. F. Mott, *A Life in Science*, (Taylor & Francis, London, 1986). ISBN 0850663334, ISBN 978-0850663334

References

- Brian Pippard, *Nevill Francis Mott*, Physics Today, March 1997, pp. 95 and 96: (pdf) [2].

External links

- Nobel lecture [3] (PDF)
- Sir Nevill Francis Mott [4]
- Mott's memories [5] University of Bristol (accessed Jan 2006)
- National Cataloguing Unit for the Archives of Contemporary Scientists [6] Bath University

References

[1] http://www.gazettes-online.co.uk/ViewPDF.aspx?pdf=42552&geotype=London&gpn=2&type=ArchivedIssuePage&all=&exact=Mott&atleast=&similar=

[2] http://scitation.aip.org/getpdf/servlet/GetPDFServlet?filetype=pdf&id=PHTOAD000050000003000095000003&idtype=cvips&prog=search

[3] http://nobelprize.org/nobel_prizes/physics/laureates/1977/mott-lecture.pdf

[4] http://www.nobel-winners.com/Physics/nevill_francis_mott.html

[5] http://www.phy.bris.ac.uk/history/11.%20Mott's%20Memories.pdf

[6] http://www.bath.ac.uk/ncuacs/rslp-nfm.htm

Erwin Schrödinger

<table>
<tr><td colspan="2" align="center">Erwin Schrödinger</td></tr>
<tr><td colspan="2" align="center"></td></tr>
<tr><td>Born</td><td>Erwin Rudolf Josef Alexander Schrödinger
12 August 1887
Erdberg de, Vienna, Austria-Hungary</td></tr>
<tr><td>Died</td><td>4 January 1961 (aged 73)
Vienna, Austria</td></tr>
<tr><td>Citizenship</td><td>Austria, Germany, Ireland</td></tr>
<tr><td>Nationality</td><td>Austria</td></tr>
<tr><td>Fields</td><td>Physics</td></tr>
<tr><td>Institutions</td><td>University of Breslau
University of Zürich
Humboldt University of Berlin
University of Oxford
University of Graz
Dublin Institute for Advanced Studies
Ghent University</td></tr>
<tr><td>Alma mater</td><td>University of Vienna</td></tr>
<tr><td>Doctoral advisor</td><td>Friedrich Hasenöhrl</td></tr>
<tr><td>Other academic advisors</td><td>Franz S. Exner
Friedrich Hasenöhrl</td></tr>
<tr><td>Notable students</td><td>Linus Pauling
Felix Bloch</td></tr>
<tr><td>Known for</td><td>Schrödinger equation
Schrödinger's cat
Schrödinger method
Schrödinger functional
Schrödinger picture
Schrödinger-Newton equations
Schrödinger field
Rayleigh-Schrödinger perturbation
Schrödinger logics
Cat state</td></tr>
<tr><td>Notable awards</td><td>Nobel Prize in Physics (1933)</td></tr>
<tr><td colspan="2" align="center">Signature
</td></tr>
</table>

Erwin   Rudolf   Josef   Alexander   Schrödinger (German pronunciation: [ˈɛrviːn ˈʃrøːdɪŋɐ]; 12 August 1887, Erdberg − 4 January 1961, Vienna) was an Austrian theoretical physicist who achieved fame for his contributions to quantum mechanics, especially the Schrödinger equation, for which he received the Nobel Prize in 1933. In 1935, after extensive correspondence with personal friend Albert Einstein, he proposed the Schrödinger's cat thought experiment.

Bust of Schrödinger, in the courtyard arcade of the main building, University of Vienna, Austria.

Biography

Early years

In 1887 Schrödinger was born in Vienna, Austria to **Rudolf Schrödinger** (cerecloth producer, botanist) and **Georgine Emilia Brenda** (daughter of **Alexander Bauer**, Professor of Chemistry, k.u.k. Technische Hochschule Vienna).

His mother was half Austrian and half English; the English side of her family came from Leamington Spa. Schrödinger learned English and German almost at the same time due to the fact that both were spoken in the family household. His father was a Catholic and his mother was a Lutheran.

In 1898 he attended the Akademisches Gymnasium. Between 1906 and 1910 Schrödinger studied in Vienna under Franz Serafin Exner (1849 - 1926) and Friedrich Hasenöhrl (1874 - 1915). He also conducted experimental work with K.W.F. Kohlrausch.[1] In 1911, Schrödinger became an assistant to Exner. At an early age, Schrödinger was strongly influenced by Schopenhauer[2] . As a result of his extensive reading of Schopenhauer's works, he became deeply interested throughout his life in color theory, philosophy[3] , perception, and eastern religion, especially Hindu Vedanta.

Middle years

In 1914 Erwin Schrödinger achieved Habilitation (*venia legendi*). Between 1914 and 1918 he participated in war work as a commissioned officer in the Austrian fortress artillery (Gorizia, Duino, Sistiana, Prosecco, Vienna). On 6 April 1920, Schrödinger married Annemarie Bertel. The same year, he became the assistant to Max Wien, in Jena, and in September 1920 he attained the position of ao. Prof. (*Ausserordentlicher Professor*), roughly equivalent to Reader (UK) or associate professor (US), in Stuttgart. In 1921, he became o. Prof. (*Ordentlicher Professor*, i.e. full professor), in Breslau (now Wrocław, Poland).

In 1921, he moved to the University of Zürich. In January 1926, Schrödinger published in the Annalen der Physik the paper "*Quantisierung als Eigenwertproblem*" [*tr.* Quantization as an Eigenvalue Problem] on wave mechanics and what is now known as the Schrödinger equation. In this paper he gave a "derivation" of the wave equation for time independent systems, and showed that it gave the correct energy eigenvalues for the hydrogen-like atom. This paper has been universally celebrated as one of the most important achievements of the twentieth century, and created a revolution in quantum mechanics, and indeed of all physics and chemistry. A second paper was submitted just four weeks later that solved the quantum harmonic oscillator, the rigid rotor and the diatomic molecule, and gives a new derivation of the Schrödinger equation. A third paper in May showed the equivalence of his approach to that of Heisenberg and gave the treatment of the Stark effect. A fourth paper in this most remarkable series showed how to treat problems in which the system changes with time, as in scattering problems. These papers were the central achievement of his career and were at once recognized as having great significance by the physics community.
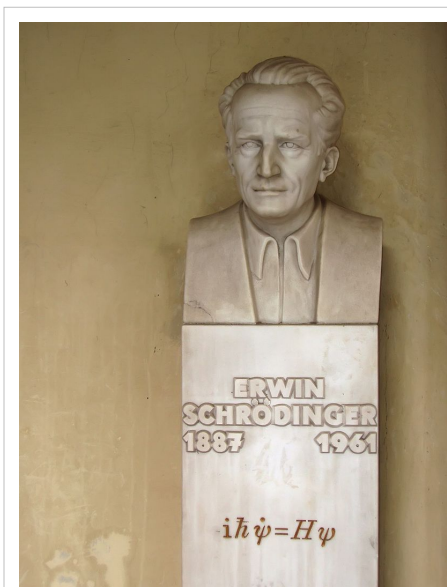
In 1927, he succeeded Max Planck at the Friedrich Wilhelm University in Berlin. In 1933, however, Schrödinger decided to leave Germany; he disliked the Nazis' anti-semitism. He became a Fellow of Magdalen College at the University of Oxford. Soon after he arrived, he received the Nobel Prize together with Paul Adrien Maurice Dirac. His position at Oxford did not work out; his unconventional personal life (Schrödinger lived with two women) was not met with acceptance. In 1934, Schrödinger lectured at Princeton University; he was offered a permanent position there, but did not accept it. Again, his wish to set up house with his wife and his mistress may have posed a problem. He had the prospect of a position at the University of Edinburgh but visa delays occurred, and in the end he took up a position at the University of Graz in Austria in 1936.

In the midst of these tenure issues in 1935, after extensive correspondence with personal friend Albert Einstein, he proposed the Schrödinger's cat thought experiment.

Later years

In 1939, after the Anschluss, Schrödinger had problems because of his flight from Germany in 1933 and his known opposition to Nazism. He issued a statement recanting this opposition (he later regretted doing so, and he personally apologized to Einstein). However, this did not fully appease the new dispensation and the university dismissed him from his job for political unreliability. He suffered harassment and received instructions not to leave the country, but he and his wife fled to Italy. From there he went to visiting positions in Oxford and Ghent Universities.

In 1940 he received an invitation to help establish an Institute for Advanced Studies in Dublin, Ireland. He moved to Clontarf, Dublin and became the Director of the School for Theoretical Physics and remained there for 17 years, during which time he became a naturalized Irish citizen. He wrote about 50 further publications on various topics, including his explorations of unified field theory.

Erwin Schrödinger in 1933

In 1944, he wrote *What is Life?*, which contains a discussion of Negentropy and the concept of a complex molecule with the genetic code for living organisms. According to James D. Watson's memoir, *DNA, the Secret of Life*, Schrödinger's book gave Watson the inspiration to research the gene, which led to the discovery of the DNA double helix structure. Similarly, Francis Crick, in his autobiographical book *What Mad Pursuit*, described how he was influenced by Schrödinger's speculations about how genetic information might be stored in molecules. However, the geneticist and 1946 Nobel-prize winner H.J. Muller had in his 1922 article "Variation due to Change in the Individual Gene"[4] already laid out all the basic properties of the heredity molecule that Schrödinger derives from first principles in *What is Life?*, properties which Muller refined in his 1929 article "The Gene As The Basis of Life"[5] and further clarified during the 1930s, long before the publication of *What is Life?*[6] .

Schrödinger stayed in Dublin until retiring in 1955. During this time he remained committed to his particular passion; involvements with students occurred and he fathered two children by two different Irish women . He had a life-long interest in the Vedanta philosophy of Hinduism, which influenced his speculations at the close of *What is Life?* about the possibility that individual consciousness is only a manifestation of a unitary consciousness pervading the universe.[7]

In 1956, he returned to Vienna (chair *ad personam*). At an important lecture during the World Energy Conference he refused to speak on nuclear energy because of his skepticism about it and gave a philosophical lecture instead. During this period Schrödinger turned from mainstream quantum mechanics' definition of wave-particle duality and promoted the wave idea alone causing much controversy.

Personal life

Schrödinger suffered from tuberculosis and several times in the 1920s stayed at a sanatorium in Arosa. It was there that he discovered his wave equation. [8]

Schrödinger decided in 1933 that he could not live in a country in which persecution of Jews had become a national policy. Alexander Frederick Lindemann, the head of physics at Oxford University, visited Germany in the spring of 1933 to try to arrange positions in England for some young Jewish scientists from Germany. He spoke to Schrödinger about posts for one of his assistants and was surprised to discover that Schrödinger himself was interested in leaving Germany. Schrödinger asked for a colleague, Arthur March, to be offered a post as his assistant.

The request for March stemmed from Schrödinger's unconventional relationships with women: although his relations with his wife Anny were good, he had had many lovers with his wife's full knowledge (and in fact, Anny had her own lover, Hermann Weyl). Schrödinger asked for March to be his assistant because, at that time, he was in love with March's wife Hilde.

Many of the scientists who had left Germany spent mid-1933 in the Italian province of Bolzano. Here Hilde became pregnant with Schrödinger's child. On 4 November 1933 Schrödinger, his wife and Hilde March arrived in Oxford. Schrödinger had been elected a fellow of Magdalen College. Soon after they arrived in Oxford, Schrödinger heard that, for his work on wave mechanics, he had been awarded the Nobel prize.

In early 1934 Schrödinger was invited to lecture at Princeton University and while there he was made an offer of a permanent position. On his return to Oxford he negotiated about salary and pension conditions at Princeton but in the end he did not accept. It is thought that the fact that he wished to live at Princeton with Anny and Hilde both sharing the upbringing of his child was not found acceptable. The fact that Schrödinger openly had two wives, even if one of them was married to another man, was not well received in Oxford either. Nevertheless, his daughter Ruth Georgie Erica was born there on 30 May 1934.[9]

On 4 January 1961, Schrödinger died in Vienna at the age of 73 of tuberculosis. He left a widow, Anny (born Annemarie Bertel on 3 December 1896, died 3 October 1965), and was buried in Alpbach, Austria.

Legacy

The philosophical issues raised by Schrödinger's cat are still debated today and remains his most enduring legacy in popular science, while Schrödinger's equation is his most enduring legacy at a more technical level. The huge crater Schrödinger, on the far side of the Moon is named after him. The Erwin Schrödinger International Institute for Mathematical Physics [10] was established in Vienna in 1993.

Color

One of Schrödinger's lesser-known areas of scientific contribution was his work on color, color perception, and colorimetry (*Farbenmetrik*). In 1920, he published three papers in this area:

Erwin Schrödinger's gravesite

- "Theorie der Pigmente von größter Leuchtkraft," *Annalen der Physik*, (4), 62, (1920), 603-622
- "Grundlinien einer Theorie der Farbenmetrik im Tagessehen," *Annalen der Physik*, (4), 63, (1920), 397-426; 427-456; 481-520 (Outline of a theory of color measurement for daylight vision)
- "Farbenmetrik," *Zeitschrift für Physik*, 1, (1920), 459-466 (Color measurement)

The second of these is available in English as "Outline of a Theory of Color Measurement for Daylight Vision" in *Sources of Color Science*, Ed. David L. MacAdam, The MIT Press (1970), 134-182.

Bibliography

- *Nature and the Greeks* and *Science and Humanism* Cambridge University Press (1996) ISBN 0521575508.
- *The interpretation of Quantum Mechanics* Ox Bow Press (1995) ISBN 1881987094.
- *Statistical Thermodynamics* Dover Publications (1989) ISBN 0486661016.
- *Collected papers* Friedr. Vieweg & Sohn (1984) ISBN 3700105738.
- *My View of the World* Ox Bow Press (1983) ISBN 0918024307.
- *Expanding Universes* Cambridge University Press (1956).
- *Space-Time Structure* Cambridge University Press (1950) ISBN 0521315204.
- *What is Life?* Macmillan (1946).
- *What is Life? & Mind and Matter* Cambridge University Press (1974) ISBN 052109397X.
- *A Life of Erwin Schrödinger*, Walter J. Moore, Cambridge University Press, Canto Edition (2003) ISBN 0521469341.

See also

- Entropy and life
- Schrödinger method
- Schrödinger functional
- List of Austrian scientists
- List of Austrians
- *Quantum Aspects of Life*
- *What is Life?*
- Subject-object problem
- Schrödinger's cat

External links

- Erwin Schrödinger on an Austrian banknote. [11]
- O'Connor, John J.; Robertson, Edmund F., "Erwin Schrödinger" [12], *MacTutor History of Mathematics archive*, University of St Andrews.
- 1927 Solvay video with opening shot of Schrödinger [13]
- " *biographie* [14]" (in German) or
- " *Biography from the Austrian Central Library for Physics* [15]" (in English)
- Encyclopaedia Britannica article on Erwin Schrodinger [16]
- Nobel Lectures, Physics 1922-1941, " *Erwin Schrödinger Biography* [17]" from NobelPrize.org
- Vallabhan, C. P. Girija, " *Indian influences on Quantum Dynamics* [18]" [ed. Schrödinger's interest in Vedanta]
- Schrödinger Medal [19] of the World Association of Theoretically Oriented Chemists (WATOC)
- *The Discovery of New Productive Forms of Atomic Theory* Nobel Banquet speech [20] (in German)
- Quantum Mechanics and Schrodinger's Cat [21]
- Annotated bibliography for Erwin Schrodinger from the Alsos Digital Library for Nuclear Issues [22]
- Schrödinger and his interest for Hinduism [23]
- Critical interdisciplinary review of Schrödinger's "What is life?" [24]

(Italian)

References

[1] Karl Grandin, ed. (1933). "Erwin Schrödinger Biography" (http://nobelprize.org/nobel_prizes/physics/laureates/1933/schrodinger-bio. html). *Les Prix Nobel*. The Nobel Foundation. . Retrieved 2008-07-29.

[2] *A Life of Erwin Schrödinger*, Chapter 4

[3] In his lecture "Mind and Matter," Chapter 4, he said that a phrase "that has become familiar to us" is "The world extended in space and time is but our representation (*Vorstellung*)." This is a repetition of the first words of Schopenhauer's main work.

[4] American Naturalist 56 (1922)

[5] Proceedings of the International Congress of Plant Sciences 1 (1929)

[6] In Pursuit of the Gene. From Darwin to DNA - By James Schwartz. Harvard University Press, 2008

[7] *My View of the World* Erwin Schroedinger chapter iv. What is life? the physical aspect of the living cell & Mind and matter - By Erwin Schrodinger

[8] *Schrödinger* by Walter J. Moore: Christmas at Arosa (http://books.google.co.uk/books?id=m-YF1glKWLoC&pg=PA194&lpg=PA194& dq=schrodinger+arosa&source=bl&ots=kc4OC4gfBO&sig=5Sc3QrQBGVpZI94s4tWw9pxXL5I&hl=en& ei=3XYdSuKTIoSsjAf9rIyRDQ&sa=X&oi=book_result&ct=result&resnum=4#PPA194,M1)

[9] *Schrödinger: Life and Thought* by Walter John Moore, Cambridge University Press 1992 ISBN 0-521-43767-9, discusses Schrödinger's unconventional relationships, including his affair with Hildegunde March, in chapters seven and eight, "Berlin" and "Exile in Oxford".

[10] http://www.esi.ac.at

[11] http://www-personal.umich.edu/~jbourj/money1.htm

[12] http://www-history.mcs.st-andrews.ac.uk/Biographies/Schrodinger.html

[13] http://uk.youtube.com/watch?v=8GZdZUouzBY

[14] http://www.zbp.univie.ac.at/schrodinger/bio/bio1.htm

[15] http://www.zbp.univie.ac.at/schrodinger/ebio/bio1.htm

[16] http://www.britannica.com/eb/article-9066219/Erwin-Schrodinger

[17] http://www.nobel.se/physics/laureates/1933/schrodinger-bio.html

[18] http://www.photonics.cusat.edu/article2.html

[19] http://www.ch.ic.ac.uk/watoc

[20] http://holiker.narod.ru/four/schrodinger-speech.html

[21] http://www.harrymaugans.com/2006/05/03/in-search-of-schrodingers-cat/

[22] http://alsos.wlu.edu/qsearch.aspx?browse=people/Schrödinger,+Erwin

[23] http://www.hinduwisdom.info/quotes21_40.htm#Q31

[24] http://www.disf.org/CosaDevoSapere/Schroedinger.asp

Ionel Solomon

<table>
<tr><td colspan="2" align="center">**Ionel Solomon, PhD.**</td></tr>
<tr><td colspan="2" align="center"></td></tr>
<tr><td colspan="2" align="center">Member of the French Academy of Sciences since 20 June 1988</td></tr>
<tr><td>**Born**</td><td>8 January 1929
Iaşi, Romania</td></tr>
<tr><td>**Citizenship**</td><td>French</td></tr>
<tr><td>**Nationality**</td><td>French</td></tr>
<tr><td>**Fields**</td><td>physicist</td></tr>
<tr><td>**Alma mater**</td><td>Paris-Sorbonne University in France</td></tr>
<tr><td>**Notable awards**</td><td>1958 Grand Prix for Research (with Anatole Abragam and J. Combrisson); 1963 The CNRS Silver Medal; 1969 Robin Prize of the French Physics Society (Societe Francaise de Physique)</td></tr>
</table>

Ionel Solomon (born 1929) is a French-Romanian physicist, Member of the French Academy of Sciences, CNRS Research Director, and Professor at the Polytechnic School in Paris.

Education

- 1949-1951 PhD, Polytechnic School (École Polytechnique) in Paris

Major scientific contributions

Ionel Solomon made major contributions to the fields of: Nuclear Magnetic Resonance (NMR)[1] , Solid state physics, Semiconductors[2] and Photovoltaics[3] . In Nuclear Magnetic Resonance he derived fundamental equations that bear his name, and specify the nuclear spin-echo response and dipole-dipole interactions in solids (the *Solomon equations*)[4] [5] .

Scientific career

- 1951-1952 Research Fellow at the University of Liverpool, UK
- 1955-1956 Research Fellow at Harvard University, USA
- 1953-1962 Researcher in the resonance Group of the Atomic Energy Commission (Commissariat Energie Atomique in Saclay)
- 1962 Director of the Laboratory for Condensed Matter (Solid-State) Physics (Laboratoire de Physique de la Matiére Condensée), at the Polytechnic School in Paris
- 1962 Head of Research at C.N.R.S.
- 1962 Head of Conferences
- 1968 CNRS Research Director
- 1973-1976 Physics Departement Head at the Polytechnic School in Paris 1973-1974 President of the Societé Française de Physique (the French Physics Society).
- 1975-1979 Professor, at the Polytechnic School in Paris
- 1976 Invited Visiting Professor at the Xerox Research Center, Palo Alto,USA

- 1980 Invited Visiting Professor at Tokyo University
- 1981-1985 Founder and Scientific Director of SOLEMS Company
- 1987 President of the Scientific Council of PHOTOTRONICS (a French-German Company for photovoltaic products)
- 1988, June 22, Elected Member of the Physics Institute of the French Academy of Sciences[6]
- Laboratory of Condensed Matter Physics

Awards and prizes

- 1958 Grand Prix for Research (with Anatole Abragam and J. Combrisson)
- 1963 The CNRS Silver Medal
- 1969 Robin Prize of the French Physics Society (Societe Francaise de Physique)
- 1972 Holweck Prize of the Institute of Physics and S.F.P (French Physics Society)
- 1981 The Y. Peyches Prize of the Academy of Sciences

References

- Résonance magnétique (1955-1965) : Découverte de la relaxation dans un système de spins couplés. Magnétomètre terrestre. Détection bolométrique de la résonance.
- Physique des Semiconducteurs (1966-1976) : L'effet Hall "extraordinaire". Pompage optique dans les solides. Découverte du transport dépendant des Spins.
- Silicium amorphe et photovoltaïque (1977-1987) : transport et optique dans le silicium amorphe. Photopiles solaires. Nouveaux matériaux amorphes.
- Recherche matériaux (depuis 1989) : fibres carbone, fibres SiC et SiCN. Photoluminescence et électroluminescence dans les semiconducteurs et dispositifs.
- I. Solomon. "Amorphous Semiconductors", In *Topics in Applied Physics*, Ed. Springer Verlag, Berlin (1979).
- I. Solomon. Relaxation Processes in a System of Two Spins. *Phys. Rev*. **99**, 559 (1955)
- I. Solomon, M.P. Schmidt, H. Tran Quoc. Selective low-power plasma decomposition of silane-methane mixtures for the preparation of methylated amorphous silicon. *Phys. Rev.* B *38, 9895 (1988)*
- I. Solomon, B. Drevillon, H. Shirai, N. Layadi. Plasma deposition of microcrystalline silicon: the selective etching model.,*J. Non-crystalline Solids*, 164-166, p. 989 (1993).
- K. Rerbal, F. Jomard, J.-N. Chazalviel, F. Ozanam, I. Solomon. Visible luminescence of porous amorphous Si(1-x) Cx:H due to selective dissolution of silicon. *Appl. Phys. lett*. **83**, p. 45 (2003)
- K. Kerbral, J.N. Chazalviel, F. Ozanam, I. Solomon. Temperature dependence of photoluminescence in amorphous Si1-xCx:H films. *Eur. Phys. J.* **B51**, p. 61 (2006).

References

[1] Résonance magnétique (1955-1965) : Découverte de la relaxation dans un système de spins couplés. Magnétomètre terrestre. Détection bolométrique de la résonance.

[2] Physique des Semiconducteurs (1966-1976) : L'effet Hall "extraordinaire". Pompage optique dans les solides. Découverte du transport dépendant des Spins.

[3] Silicium amorphe et photovoltaïque (1977-1987) : transport et optique dans le silicium amorphe. Photopiles solaires. Nouveaux matériaux amorphes.

[4] http://planetphysics.org/encyclopedia/IonelSolomon.html Biography of physicist Ionel Solomon

[5] I. Solomon. Relaxation Processes in a System of Two Spins. *Phys. Rev.* **99**: 559 (1955)

[6] http://www.academie-sciences.fr/membres/S/liste_alphabetique_S.htm Members of the French Academy of Sciences

Theodor V.Ionescu

	Theodor V. Ionescu

Acad. Prof. Dr. Th. V. Ionescu in Bucharest, 1970

Born	February 8, 1899 Dorohoi, Romania
Died	November 6, 1988 (aged 89)
Citizenship	Romania
Ethnicity	Romanian
Fields	physicist
Alma mater	Paris-Sorbonne University University of Iaşi University of Bucharest
Known for	Plasma Physics magnetic resonance first maser studies magnetron invention 3D cinematography/TV devices coupled electron-ion oscillations in ultra-hot plasmas nuclear fusion in ultra-hot hydrogen plasmas

Theodor V. Ionescu, **Prof. Dr. Doc.** (born February 8 1899, Dorohoi, Botoşani County - d. 6 November 1988, Bucharest) was a Romanian physicist and inventor who made remarkable discoveries in plasma physics, ionosphere physics, ion coupling electrons in dense plasmas, masers, magnetron amplifiers, and Zeeman effects related to controlled nuclear fusion, quantum emission mechanisms in hot plasmas. Member of the Romanian Academy.

Ph.D. studies in plasma physics

He received his Ph.D. in plasma physics first in Paris, and then in Iaşi, Romania. Thus, the history of plasma physics in Romania began in 1923 with the defense of the first PhD thesis in physics at the University of Iaşi by Theodor V. Ionescu, under the guidance of Professor Peter Bogdan. Th. V. Ionescu carried out the first experimental studies in Romania of the physics of ionized gases/plasmas.

Scientific achievements and collaborators

In 1925 invented a microphone based on thermoionic currents (currents emitted by heated bodies) and a light projector using the interference phenomenon.

Founded in the same year the first Electricity and Magnetism Laboratory, as well as the first Chair of Electricity and Magnetism in the Department of Mathematics and Physics at the University of Bucharest.

The first prototype of a precursor to the magnetron power amplifier

He built in 1934-1935 a precursor[1] to the high-power, multi-cavity magnetron that was built subsequently, in 1937-1940, by the British physicist, Sir John Turton Randall, FRSE together with a team of British coworkers for the British and American, military radar instalations in WWII[2] . At the same time, the Telefunken Company of Berlin was 'searching' for such a device[3] but has apparently met with much less success than the British inventors or Th. V. Ionescu. (However, the split anode magnetron had first been developed in 1921 by Dr. A.E.Hull at GEC Company in USA; also in 1921, Haben, who was working in Germany, developed a similar device that worked on a 3 cm wavelength. A strong competitor of the former inventors was also Dr. H.E.Hollman who registered many patents between 1925 and 1935 that documented devices related to magnetron development)[4] .

Patents

In 1936 he obtained a patent for the 3D imaging in cinema and television. In 1946, together with physicist V. Mihu invented and built a device that has obtained the first 'show boosted " type maser (*microwave quantum amplifier*), and has thus tested the first precursor of the working maser [5] reported in 1954[6] .

Discoveries

He worked in the early 1960s in the Laboratory of the Bucharest Institute of Plasma Physics together with his childhood friend, Octav Gheorghiu [7], whom he greatly respected for his exceptional human qualities. They studied systematically the resonant frequencies of molecular oxygen and hydrogen ions. Then, they published their most important experimental results in a series of articles in *C.R. Acad. Sci. Paris".(pp.245, 898, 957, 246, pp. 2250, 3598, 1958, 250, 2182 p. 1960, 252, p. 870, 1961) and* Rev Roum. Phys.

In the early 1970s, together with physicists Dr. Radu Pârvan and J. C. Băianu [8] - one of his Ph.D. research assistants in plasma physics in magnetic fields in the Electricity Department of the Faculty of Physics, Bucharest - Th. V. Ionescu completed experiments on controlled magnetic resonance oscillations in ultra-hot plasmas. Such seminal experiments involved the coupling of ionic and electronic oscillations in ultra-hot plasma involving quantum amplified stimulation processes in the presence of longitudinal magnetic fields which opened novel possibilities for achieving hot nuclear fusion in the future (Achieving nuclear fusion in high pressure hot plasma [9])[10] . The first report of these research results was presented at the French Academy of Science in Paris by Louis Néel, member of the Academy and Nobel Prize in Physics for Magnetism[11] . Additional results were then published in the same year in the internationally renowned magazine *C.R. Acad. Sci. Paris*[12] .

His successor as Head of Department in 1970 was Florin Ciorăscu, "imported" from the IFA, (who died in 1977 during the major earthquake in Bucharest).

References

- Th.V.Ionescu. *Electricity and Magnetism*. "Electricitate şi Magnetism". "Electricity and Magnetism". Course Notes., School of Physics, University of Bucharest., 1960.

- Th.V.Ionescu et al. (1969). "Les oscillations ioniques dans les cathodes creuses dans un champ magnetique.", transmise par M. Louis Neel, *C.R.A.Sci. Paris*, **270**: 1321-1324,

- Gh. Popa, L. Sîrghi, *Fundamentals of plasma physics* (*Bazele fizicii plasmei*), Ed. Univ.Course Notes., Department of Physics, University of Bucharest., 1960.

- *Romanian personalities of science and technology - the dictionary*, Scientific and Encyclopaedic Publishing House, Bucharest, 1982

- Ioan Ioviţ Popescu, D. Ciobotaru, *Bazele fizicii plasmei.*, Ed. Tehnică, Bucureşti, 1987.

- D.Alexandroaei, *Special Chapters in Plasma Physics.* (*Capitole speciale de fizica plasmei.*), Ed. Univ."Al.I.Cuza", Iasi, 2000.

- Nicoleta Dumitrascu, *Introduction to plasma physics* (*Introducere în fizica plasmei.*), Ed Junimea 1999 * John Ioviţă Popescu, D. Ciobotaru, "Fundamentals of plasma physics", Technical Publishing House, Bucharest, 1987.

- *Personalităţi româneşti ale ştiinţelor naturii şi tehnicii - dicţionar*, Ed. Ştiinţifică şi Enciclopedică, Bucureşti, 1982

References

[1] Th.V.Ionescu. *Electricity and Magnetism* ("Electricitate şi Magnetism"): Course Notes., School of Physics, University of Bucharest., (1960), pp.1247

[2] "Radar Recollections - A Bournemouth University/CHiDE/HLF project" by Prof. W. E. Burcham (http://histru.bournemouth.ac.uk/Oral_History/Talking_About_Technology/radar_research/the_magnetron.html)

[3] From the 1935 magazine *Electronics*: "Microwaves To Detect Aircraft" (http://histru.bournemouth.ac.uk/Oral_History/Talking_About_Technology/radar_research/the_magnetron.html)

[4] "Radar Recollections - A Bournemouth University/CHiDE/HLF project" (http://histru.bournemouth.ac.uk/Oral_History/Talking_About_Technology/radar_research/the_magnetron.html)

[5] http://einstein.stanford.edu/content/faqs/maser.html

[6] http://en.wikipedia.org/wiki/Maser

[7] http://alpha1.infim.ro/rrp/2005_57_1/Gheorghiu.pdf

[8] http://ro.wikipedia.org/wiki/List%C4%83_de_biofizicieni_rom%C3%A2nia

[9] http://nobelprize.org/nobel_prizes/physics/laureates/1978/kapitsa-lecture.html

[10] http://nobelprize.org/nobel_prizes/physics/laureates/1978/kapitsa-lecture.pdf PLASMA AND THE CONTROLLED THERMONUCLEAR REACTION

[11] http://nobelprize.org/nobel_prizes/physics/laureates/1970/neel-lecture.html Louis Néel: "Magnetism and the Local Molecular Field"

[12] Th.V.Ionescu et al. (1969). *C.R.A.Sci. Paris*, **270**: 1321-1324

Herbert S.Gutowsky

Herbert S. Gutowsky	
Professor Herbert S. Gutowsky, Member of the US National Academy of Sciences	
Born	November 8, 1919 Bridgman, Michigan
Died	January 13, 2000 Urbana
Citizenship	USA
Nationality	USA
Ethnicity	US
Fields	Nuclear magnetic resonance
Institutions	University of Illinois at Urbana
Alma mater	Harvard University
Doctoral advisor	George Kistiakowsky
Doctoral students	35
Known for	Solid-state NMR and NMR spectroscopy
Notable awards	Kistiakowsky prize, Wolf prize, Irving Langmuir prize, Peter Debye prize, Member of the National Academy of Sciences, USA.

Herbert S. Gutowsky (November 8, 1919 - January 13, 2000) was an American chemist who was a Professor of Chemistry at the University of Illinois at Urbana-Champaign. His pioneering work made nuclear magnetic resonance spectroscopy one of the most effective tools in chemical and medical research.

Birth and education

Herbert S. Gutowsky was born on November 8, 1919, on a produce farm in Bridgman, Michigan. He was the son of Otto and Hattie Neyer Gutowsky. He claimed that his childhood experiences taught him the importance of hard work, which carried over to his scientific life. He was a quiet, kind and thoughtful man who focused on science and who worked very closely with all his research associates. He was also an avid bicyclist in his early life, and also bird-watcher who later became very interested in growing roses in his own garden.

Gutowsky received a bachelor's degree from Indiana University in 1940, and after a four-year interruption for military service, he was awarded a master's degree from UC-Berkeley in 1946. Gutowsky earned his Ph.D. in chemistry from Harvard University under George Kistiakowsky.

Academic career

He joined the faculty of the University of Illinois at Urbana-Champaign in 1948. He became a full professor in 1956. His research interests as a young faculty member included molecular and solid-state structure by infrared (IR) and radio frequency spectroscopy, including both nuclear magnetic resonance and electron paramagnetic resonance.

Research on Nuclear Magnetic Resonance

Herbert S. Gutowsky was the first to apply the nuclear magnetic resonance method to chemical research. His experimental and theoretical work on the chemical shift effect and its relation to molecular structure has provided the chemist with working tools to study molecular conformation and molecular interactions in solutions. Gutowsky's pioneering work on the spin-spin coupling effect developed this phenomenon into a 'finger print' method for the identification and characterization of organic compounds. He was also the first to observe the effect of dynamic processes on the lineshape of high resolution nuclear magnetic resonance spectra, and exploited it for the studies of hindered rotation in molecules, Simultaneously with others he discovered the effect of the scalar and dipolar interaction with unpaired electrons in solutions of paramagnetic ions[1].

He was awarded the Wolf Prize in Chemistry in 1983/84 for "his pioneering work in the development and applications of nuclear magnetic resonance spectroscopy in chemistry"[2]. More specifically, the latter prize committee cited explicitly his truly outstanding physical chemistry research results as follows: "*Professor Herbert S. Gutowsky was the first to apply the nuclear magnetic resonance method to chemical research. His experimental and theoretical work on the chemical shift effect and its relation to molecular structure has provided the chemist with working tools to study molecular conformation and molecular interactions in solutions. Gutowsky's pioneering work on the spin-spin coupling effect developed this phenomenon into a 'finger print' method for the identification and characterization of organic compounds. He was also the first to observe the effect of dynamic processes on the lineshape of high resolution nuclear magnetic resonance spectra, and exploited it for the studies of hindered rotation in molecules, Simultaneously with others he discovered the effect of the scalar and dipole-dipole interaction with unpaired electrons in solutions of paramagnetic ions*."

Later years

He became head of the Department of Chemistry at the University of Illinois at Urbana-Champaign in 1967, and in 1970 he oversaw the creation of the School of Chemical Sciences, which included the departments of chemistry and chemical engineering. He served as Director of the School of Chemical Sciences from 1970 to 1983.

During 1976--1986 he published in collaboration with a photosynthesis research group in the Biophysics Department the results of a series of NMR, fluorescence, pulsed light/oxygen evolution studies of biomembranes-- including photosynthetic plant membranes/thylakoids[3] [4] [5] and living, green algae[6] --investigating the complex physico-chemical mechanisms of photosynthesis involving Mn^{+2}, Mn^{+3}, Cl^- and Br^- ionic effects in photosynthetic oxygen evolution and photosynthetic water oxidation by photosytem II (PS-II) in the oxygen evolving complex (OEC)[7].

After 1983 he focused on teaching and research, moving into a `third research career' in Fourier-transform microwave spectroscopy studies of small, weakly bonded molecules in the gas phase. He died on January 13, 2000 in Urbana.

Other Heads, Department of Chemistry, University of Illinois

Head	Years of Service	Years
A. P. S. Stewart	1868-1874	6
Henry A. Weber	1874-1882	8
William McMurtrie	1882-1888	6
J. C. Jackson	1888	1
Arthur W. Palmer	1889-1904	15
Harry S. Grindley	1904-1907	3
William A. Noyes	1907-1926	19
Roger Adams	1926-1954	28
Herbert E. Carter	1954-1967	13
Herbert S. Gutowsky	1967-1983	16
Larry R. Faulkner	1984-1989	5
Gary B. Schuster	1989-1994	5
Paul W. Bohn	1995-1999	5
Steven C. Zimmerman	1999-2000	1
Gregory S. Girolami	2000-2005	5
Steven C. Zimmerman	2005-	

See also

- Charles Pence Slichter
- Nuclear magnetic resonance
- Chemical shift
- Knight shift
- Relaxation
- J-coupling
- Dynamic nuclear polarisation
- NMR spectroscopy
- Carbon-13 NMR
- Deuterium NMR
- 2D-FT NMRI and Spectroscopy
- Solid-state nuclear magnetic resonance
- NMR spectra database
- In vivo magnetic resonance spectroscopy

External links

- Biography of Herbert S. Gutowsky [8]
- Herbert S. Gutowsky and NMR Spectroscopy [9]
- Nuclear Magnetic Resonance in Physical Chemistry [10]

References

[1] Research on Nuclear Magnetic Resonance by Herbert S. Gutowsky (http://www.wolffund.org.il/full.asp?id=47)

[2] The Wolf Prize in Chemistry (http://www.wolffund.org.il/cat.asp?id=15&cat_title=CHEMISTRY)

[3] http://www.pnas.org/cgi/content/abstract/81/12/3713?ck=nck

[4] NMR study of chloride ion interactions with thylakoid membranes. PNAS, June 1, 1984, vol. 81, no. 12, 3713-3717, I. C. Baianu, C. Critchley, Govindjee and H. S. Gutowsky

[5] http://www.life.illinois.edu/govindjee/pubschron.html W.J. Coleman, I.C. Baianu, H.S. Gutowsky and Govindjee (1984) The Effect of Chloride and Other Anions on the Thermal Inactivation of Oxygen Evolution in Spinach Chloroplasts. In: C. Sybesma (ed.) Advances in Photosynthesis Research, Martinus Nijhoff/Dr. W. Junk Publishers, Den Haag, pp. 283-286

[6] http://www.life.illinois.edu/govindjee/pubschron.html Govindjee, I.C. Baianu, C. Critchley and H.S. Gutowsky (1983) Comments on the Possible Roles of Bicarbonate and Chloride Ions in Photosystem II. In: Y. Inoue, A.R. Crofts, Govindjee, N. Murata, G. Renger and K. Satoh (eds.) The Oxygen Evolving System of Photosynthesis. Academic Press, Tokyo and San Diego, pp. 303-315

[7] http://www.life.illinois.edu/govindjee/pubschron.html C. Critchley, I.C. Baianu, Govindjee and H.S. Gutowsky(1982) The Role of Chloride in O2 Evolution by Thylakoids from Salt-tolerant Higher Plants. Biochim. Biophys. Acta 682: 436-445.

[8] http://chemistry.illinois.edu/about/illini_chemists/Herbert_Gutowsky.html

[9] http://acswebcontent.acs.org/landmarks/landmarks/noyes/gutowsky.html

[10] http://planetphysics.org/?op=getobj&from=books&id=290

Erwin Hahn

Erwin Hahn	
No free image Do you own one? If so, please click here	
Born	June 9, 1921 Sharon, Pennsylvania
Fields	Physics
Institutions	University of California, Berkeley

Erwin L. Hahn (born 1921) is a U.S. physicist, best known for his work on nuclear magnetic resonance (NMR).[1] In 1950 he discovered the spin echo.

He received his B.S. in Physics from Juniata College. He has been Professor Emeritus at the University of California, Berkeley since 1991 and was professor of physics, 1955-91.

See also

- *Pulsed magnetic resonance--NMR, ESR, and optics: a recognition of E.L. Hahn*. Oxford University Press. 1992. ISBN 0198539622.

External links

- Oral History interview transcript with Erwin L. Hahn 21 August 1986, American Institute of Physics, Niels Bohr Library and Archives [2]

References

[1] Filler, AG: The history, development, and impact of computed imaging in neurological diagnosis and neurosurgery: CT, MRI, DTI: Nature Precedings DOI: 10.1038/npre.2009.3267.4 (http://precedings.nature.com/documents/3267/version/4).

[2] http://www.aip.org/history/ohilist/4652.html

Peter Mansfield

<table>
<tr><td colspan="2" align="center">**Peter Mansfield**</td></tr>
<tr><td colspan="2" align="center"></td></tr>
<tr><td>**Born**</td><td>9 October 1933</td></tr>
<tr><td>**Nationality**</td><td>British</td></tr>
<tr><td>**Institutions**</td><td>University of Nottingham</td></tr>
<tr><td>**Known for**</td><td>Magnetic Resonance Imaging</td></tr>
<tr><td>**Notable awards**</td><td>Nobel Prize in Physiology or Medicine (2003)</td></tr>
</table>

Sir Peter Mansfield, FRS, (born 9 October 1933), is a British physicist who was awarded the 2003 Nobel Prize in Physiology or Medicine for his discoveries concerning magnetic resonance imaging (MRI). The Nobel Prize was shared with Paul Lauterbur, who also contributed to the development of MRI. Sir Peter is a professor at the University of Nottingham.

The Nobel Prize in Physics in 1952, which went to Felix Bloch and Edward Purcell, was for the development of nuclear magnetic resonance (NMR), the scientific principle behind MRI. For decades magnetic resonance was used mainly for studying the chemical structure of substances, and Mansfield's first project in this field was to develop a portable, transistorised Earth's field NMR (EFNMR) spectrometer in the late 1950s. It was not until the 1970s with Lauterbur's and Mansfield's developments that NMR could be used to produce images of the body. Mansfield is credited with showing how the radio signals from MRI can be mathematically analyzed, making interpretation of the signals into a useful image a possibility. He is also credited with discovering how fast imaging could be possible by developing the MRI protocol called echo-planar imaging. Echo-planar imaging allows T2* weighted images to be collected many times faster than previously possible. It also has made functional magnetic resonance imaging (fMRI) feasible.

Mansfield came from humble beginnings in South East London, attending secondary school in Peckham. He left school at 15, and became a printer. He took A levels in night school. He then studied physics at Queen Mary College, London, graduating with a BSc in 1959 and a PhD in 1962.[1]

He has worked in the Department of Physics at the University of Nottingham since 1964.

External links

- University of Nottingham: Peter Mansfield homepage [2]
- Nobel Prize 2003 Press Release [3]
- Appearance [4] on Desert Island Discs
- Peter Mansfield US Patents [5]
- Peter Mansfield autobiography [6]

References

[1] "Queen Mary, University of London Notable Alumni and Staff" (http://www.qmul.ac.uk/alumni/alumninetwork/notablealumni/index. html). . Retrieved 2007-09-23.

[2] http://www.magres.nottingham.ac.uk/~mansfield/

[3] http://nobelprize.org/medicine/laureates/2003/press.html

[4] http://www.bbc.co.uk/radio4/factual/desertislanddiscs_20060618.shtml

[5] http://www.patentgenius.com/inventor/MansfieldPeter.html

[6] http://nobelprize.org/nobel_prizes/medicine/laureates/2003/mansfield-autobio.html

Paul Lauterbur

Paul Lauterbur	
Born	May 6, 1929 Sidney, Ohio
Died	March 27, 2007 (aged 77)
Residence	United States
Institutions	State University of New York at Stony Brook University of Illinois at Urbana-Champaign Carnegie Mellon University
Alma mater	Case Western Reserve University University of Pittsburgh
Known for	Magnetic Resonance Imaging
Notable awards	Nobel Prize in Physiology or Medicine (2003)

Paul Christian Lauterbur (May 6, 1929 – March 27, 2007) was an American chemist who shared the Nobel Prize in Physiology or Medicine in 2003 with Peter Mansfield for his work which made the development of magnetic resonance imaging (MRI) possible.[1]

Dr. Lauterbur was a professor along with his wife Joan at the University of Illinois at Urbana-Champaign for 22 years until his death in Urbana. He never stopped working with undergraduates on research, and he served as a professor of chemistry, with appointments in bioengineering, biophysics and computational biology at the Center for Advanced Study.[2]

Early life

Born and raised in Sidney, Ohio, Lauterbur graduated from Sidney High School, where a new Chemistry, Physics, and Biology wing was dedicated in his honor. He did his undergraduate work at Case Institute of Technology in Cleveland, which is now known as Case Western Reserve University. As a teenager, he built his own laboratory in the basement of his parents' house.[3] His chemistry teacher at school understood that he enjoyed experimenting on his own, so the teacher allowed him to do his own experiments at the back of class.[3] When he was drafted into the Army in the 1950s, his superiors allowed him to spend his time working on an early nuclear magnetic resonance (NMR) machine; he had published four scientific papers by the time he left the Army.[3]

The development of the MRI

Lauterbur is a 1962 graduate of the University of Pittsburgh and credits the idea of the MRI to a brainstorm one day at a suburban Pittsburgh Big Boy, with the MRI's first model scribbled on a table napkin.[4] [3] The further research that led to the Nobel Prize was performed at Stony Brook University[5] in the 1970s.

The Nobel Prize in Physics in 1952, which went to Felix Bloch and Edward Purcell, was for the development of nuclear magnetic resonance (NMR), the scientific principle behind MRI. However, for decades magnetic resonance was used mainly for studying the chemical structure of substances. It wasn't until the 1970s with Lauterbur's and Mansfield's developments that NMR could be used to produce images of the body.

Lauterbur is credited for the idea of introducing gradients in the magnetic field which allows for determining the origin of the radio waves emitted from the nuclei of the object of study. This spatial information allows two-dimensional pictures to be produced.[3]

While Lauterbur conducted his work at Stony Brook, the best NMR machine on campus belonged to the chemistry department; he would have to visit it at night to use it for experimentation and would carefully change the settings so that they would return to those of the chemists' as he left.[6] A replica of his original MRI machine is located at the Chemistry building on the campus of the State University of New York at Stony Brook in Stony Brook, New York.

Some of the first images taken by Lauterbur included those of a clam his daughter had collected on the beach at the Long Island Sound, green peppers[3] and two test tubes of heavy water within a beaker of ordinary water; no other imaging technique in existence at that time could distinguish between two different kinds of water. The human body consists mostly of water.[6]

When Lauterbur first submitted his paper with his discoveries to *Nature*, the paper was rejected by the editors of the journal. Lauterbur persisted and requested them to review it again, upon which time it was published and is now acknowledged as a classic *Nature* paper.[7] The *Nature* editors pointed out that the pictures accompanying the paper were too fuzzy, although they were the first images to show the difference between heavy water and ordinary water.[3] Lauterbur said of the initial rejection: "You could write the entire history of science in the last 50 years in terms of papers rejected by *Science* or *Nature*."[6]

Peter Mansfield of the University of Nottingham in the United Kingdom took Lauterbur's initial work another step further, developing a mathematical process to speed the image reading.[6]

Lauterbur attempted to file patents related to his work to commercialize it unsuccessfully.[8] Stony Brook chose not to pursue patents, thinking that the expense would not pay off in the end. "The company that was in charge of such applications decided that it would not repay the expense of getting a patent. That turned out not to be a spectacularly good decision," Lauterbur said in 2003. He attempted to get the federal government to pay for an early prototype of the MRI machine for years in the 1970s, and the process took a decade.[9] The University of Nottingham did file patents which later made Mansfield wealthy.[9]

Nobel Prize

Lauterbur was awarded the Nobel Prize along with Mansfield in the fall of 2003. Controversy occurred when Raymond Damadian took out full-page ads in *The New York Times*, *The Washington Post* and *The Los Angeles Times* headlined "The Shameful Wrong That Must Be Righted" saying that the Nobel committee had not included him as a Prize winner alongside Lauterbur and Mansfield for his early work on the MRI. Damadian claimed that he discovered MRI and the two Nobel-winning scientists refined his technology. *The New York Times* published an editorial saying that while scientists credit Damadian for holding an early patent in MRI technology, Lauterbur and Mansfield conducted the work that led

U.S. President George W. Bush with the six 2003 American Nobel laureates in the Oval Office. From left to right, Dr. Roderick MacKinnon, New York City (chemistry); Dr. Anthony Leggett, Urbana, Illinois (physics); Dr. Robert Engle, New York City (economics); Dr. Alexei Abrikosov, Argonne, Illinois (physics); Dr. Peter Agre, Baltimore, Maryland (chemistry); and Dr. Paul Lauterbur, Urbana, Illinois (physiology/medicine).

to present MRI technology. The newspaper pointed out a few cases in which precursor discoveries had been awarded with a Nobel, along with a few deserving cases in which it had not, such as Rosalind Franklin and Oswald Avery.[10] [11]

Death

Lauterbur died in March 2007 of kidney disease at his home in Urbana, Illinois. University of Illinois Chancellor Richard Herman said, "Paul's influence is felt around the world every day, every time an MRI saves the life of a daughter or a son, a mother or a father."[11]

Other awards and honors

- Albert Lasker Award for Clinical Medical Research, 1984
- General Motors Cancer Research Foundation Kettering Prize, 1985
- National Medal of Science, 1987
- National Medal of Technology, 1988, (with Raymond Damadian)[8]
- Bower Award, Franklin Institute of Philadelphia, 1990 (first recipient)
- Carnegie Mellon Dickson Prize in Science in 1993.[2]
- Charter member, Phi Kappa Tau Hall of Fame in 2006.
- National Inventors Hall of Fame, class of 2007

Honorary Degrees:

- Carnegie-Mellon University in Pittsburgh
- University of Liège in Belgium
- Nicolaus Copernicus University Medical School in Kraków, Poland

See also

• Nobel Prize controversies

External links

• Nobel Prize 2003 Press Release [3]
• University of Pittsburgh Medical School article on alumnus Lauterbur [12]
• Paul C. Lauterbur Patents [13]
• Paul Lauterbur [14] at Find a Grave
• [15] Article on MRI

References

[1] Filler, AG: The history, development, and impact of computed imaging in neurological diagnosis and neurosurgery: CT, MRI, DTI: Nature Precedings DOI: 10.1038/npre.2009.3267.4 (http://precedings.nature.com/documents/3267/version/4).

[2] Spice, Byron (2003-10-07). "Nobel Prize for MRI began with a burger in New Kensington" (http://www.post-gazette.com/pg/03280/ 228666.stm). *Pittsburgh Post-Gazette*. . Retrieved 2007-08-05.

[3] "Paul Lauterbur" (http://www.economist.com/obituary/displaystory.cfm?story_id=8954439). *The Economist*. 2007-04-07. . Retrieved 2007-08-04.

[4] http://www.umc.pitt.edu/pittmag/fall2004/feature1.html

[5] Nobel Prize Awardee Paul Lauterbur Returns To SBU Where His Winning Research Was Conducted In The '70s (http://commcgi.cc. stonybrook.edu/cgi-bin/artman/exec/view.cgi?archive=5&num=755)

[6] Wade, Nicholas (2003-10-07). "American and Briton Win Nobel for Using Chemists' Test for M.R.I.'s" (http://query.nytimes.com/gst/ fullpage.html?sec=health&res=9800EFDC103CF934A35753C1A9659C8B63). *New York Times*. . Retrieved 2007-08-04.

[7] "MRI — a new way of seeing" (http://www.nature.com/physics/looking-back/lauterbur/index.html). *Nature*. . Retrieved 2007-08-04.

[8] Deutsch, Claudia (2007-04-07). "Patent Fights Aplenty for M.R.I. Pioneer" (http://query.nytimes.com/gst/fullpage. html?res=9906E0DF1F39F931A25754C0A961958260&sec=&spon=&pagewanted=print). *New York Times*. . Retrieved 2007-08-04.

[9] Maugh, Thomas (2007-04-07). "Paul Lauterbur, 77; 'the father of MRI'" (http://www.latimes.com/news/science/ la-me-lauterbur28mar28,1,7609292.story?track=rss&ctrack=1&cset=true). *Los Angeles Times*. . Retrieved 2007-08-04.

[10] Judson, Horace (2003-10-20). "No Nobel Prize for Whining" (http://query.nytimes.com/gst/fullpage.html?sec=health& res=9C02E4DE123EF933A15753C1A9659C8B63). *New York Times*. . Retrieved 2007-08-03.

[11] Chang, Kenneth (2007-03-28). "Paul Lauterbur, MRI pioneer and Nobel Laureate, dies" (http://www.iht.com/articles/2007/03/28/ news/obits.php). *International Herald Tribune*. . Retrieved 2007-08-04.

[12] http://www.umc.pitt.edu/pittmag/fall2004/feature1.html

[13] http://www.patentgenius.com/inventor/LauterburPaulC.html

[14] http://www.findagrave.com/cgi-bin/fg.cgi?page=gr&GRid=18681702

[15] http://www.vigyanprasar.gov.in/comcom/feature69.htm

Alberte Pullman

Alberte Pullman (née Bucher) was born in France in 1920. She is a theoretical and quantum chemist. She studied at the Sorbonne starting in 1938. During her studies she worked on calculations at Centre National de la Recherche Scientifique (CNRS). From 1943 she worked with Raymond Daudel. She completed her doctorate in 1946. On his return from war service in 1946, she married Bernard Pullman. She and her husband worked together until his death in 1996. Together they wrote several books including *Quantum Biochemistry*, Interscience Publishers, 1963. Their work in the 1950s and 1960s was the beginning of the new field of Quantum Biochemistry. They pioneered the application of quantum chemistry to predicting the carcinogenic properties of aromatic hydrocarbons.

She is a member of the International Academy of Quantum Molecular Science and a member and former President of The International Society of Quantum Biology and Pharmacology.[1]

External links

- An interview with Mme Prof. Dr. Alberte Pullman [2]

References

[1] Members of IAQMS (http://www.iaqms.org/IAQMS.members.html)

[2] http://www.quantum-chemistry-history.com/Pull1.htm

Bernard Pullman

Bernard Pullman (March 19, 1919, Wloclawek Poland -- 1996) was a French theoretical quantum chemist and quantum biochemist.

Pullman studied at the Sorbonne, then spent the Second World War as a French Army officer in Africa and the Middle East. Returning to Paris in 1946, he completed the Licence-es-Sciences in 1946 and the Docteur-es-Science in 1948. From 1946 to 1954, he worked at the Centre National de la Recherche Scientifique (CNRS). In 1954 he was appointed Professor at the Sorbonne. In 1959, he became Director of the Department of Quantum Biochemistry at the Institut de Biologie Physico-Chimique. In 1963, he was promoted to Director of the Institute. He was a founding member of the International Academy of Quantum Molecular Science.

Over the course of his career, Pullman published about 400 scientific papers and 5 books, three with his wife Alberte Pullman, his lifelong collaborator. In joint work published in the 1950s and 1960s, they founded the new field of quantum biochemistry. They also pioneered the application of quantum chemistry to predicting the carcinogenic properties of aromatic hydrocarbons.

After his 1989 retirement, he wrote *The Atom in the History of Human Thought* (Paris: Fayard, 1995), a work approachable by general readers.

References

- *International Journal of Quantum Chemistry* 75(3), 1999, Special Issue: In Memory of Bernard Pullman.

Books by Pullman

- 1963 (with Alberte Pullman). *Quantum Biochemistry*. New York: John Wiley Interscience. ISBN 9780470702314 ; ISBN 0470702311.
- 1965 (with M. Weissbluth). *Molecular Biophysics.* New York: Academic Press, New York.
- 1998. *The Atom in the History of Human Thought*, trans. by Axel Reisinger. Oxford Univ. Press.

External links

- His International Academy of Quantum Molecular Science page [1]
- An interview with Mme Prof. Dr. Alberte Pullman [2]

References

[1] http://www.iaqms.org/DeceasedMembers/IAQMS.member.PullmanB.html

Herbert Fröhlich

<table>
<tr><td colspan="2" align="center">**Herbert Fröhlich**</td></tr>
<tr><td colspan="2" align="center">
Herbert Fröhlich (1905-1991)</td></tr>
<tr><td>**Born**</td><td>9 December 1905
Rexingen, Germany</td></tr>
<tr><td>**Died**</td><td>23 January 1991 (aged 86)
Liverpool, England</td></tr>
<tr><td>**Residence**</td><td>UK</td></tr>
<tr><td>**Nationality**</td><td>British</td></tr>
<tr><td>**Ethnicity**</td><td>Jewish-German</td></tr>
<tr><td>**Fields**</td><td>Physicist</td></tr>
<tr><td>**Institutions**</td><td>University of Bristol
University of Liverpool
University of Salford
Ioffe Physico-Technical Institute
University of Freiburg
University of Bristol</td></tr>
<tr><td>**Alma mater**</td><td>Ludwig-Maximilians University</td></tr>
<tr><td>**Doctoral advisor**</td><td>Arnold Sommerfeld</td></tr>
<tr><td>**Doctoral students**</td><td>Sebastian Doniach
Gerard Hyland</td></tr>
<tr><td>**Other notable students**</td><td>Sigurd Zienau</td></tr>
<tr><td>**Known for**</td><td>Fröhlich coherence
Fröhlich polaron
Fröhlich Hamiltonian
Fröhlich term</td></tr>
<tr><td>**Notable awards**</td><td>Max-Planck Medal (1972)</td></tr>
<tr><td colspan="2" align="center">**Signature**
</td></tr>
<tr><td colspan="2">**Notes**
He is the brother of the mathematician Albrecht Fröhlich.</td></tr>
</table>

Herbert Fröhlich (9 December 1905 in Rexingen, Germany − 23 January 1991 in Liverpool, England) was a German-born British physicist and a Fellow of the Royal Society.

Fröhlich was the son of Fanny Frida (née Schwarz) and Jakob Julius Fröhlich, members of an old-established Jewish family.

Career

In 1927, Fröhlich entered the Ludwig-Maximilians University, Munich, to study physics, and he received his doctorate under Arnold Sommerfeld, in 1930.[1] His first position was as Privatdozent at the University of Freiburg. Due to rising anti-Semitism and the Deutsche Physik movement under Adolf Hitler, and at the invitation of Yakov Frenkel, Fröhlich went to the Soviet Union, in 1933, to work at the Ioffe Physico-Technical Institute in Leningrad. During the Great Purge following the murder of Sergey Kirov, he fled to England in 1935. Except for a short visit to Holland and a brief internment during World War II, he worked in Nevill Francis Mott's department, at the University of Bristol, until 1948, rising to the position of Reader. At the invitation of James Chadwick, he took the Chair for Theoretical Physics at the University of Liverpool.

He was offered by the Bell Telephone Laboratories a handsome salary to go to Princeton University as their specially endowed professor. But at Liverpool he had a purely research post, which was attractive to him, and he was newly married to an American postgraduate philosophy student, and later an artist, Fanchon Aungst, who was not keen to return to America at that time.

From 1973, he was Professor of Solid State Physics at the University of Salford, however, all the while maintaining an office at the University of Liverpool, where he gained emeritus status in 1976 until his death. During 1981, he was a visiting professor at Purdue University.[2] [3] [4]

Fröhlich proposed a theory which is known as Fröhlich coherence.[5] [6]

Honours

- 1951 – Fellow of the Royal Society
- 1972 – Deutsche Physikalische Gesellschaft Max-Planck Medal

Books

- Herbert Fröhlich *Elektronentheorie der Metalle. (Struktur und Eigenschaften der Materie in Eigendarstellung, Bd.18).* (Springer, 1936, 1969)
- Herbert Fröhlich *Elektronentheorie der Metalle* (Ann Arbor: Edwards Brothers, First US edition, in German, 1943) ISBN 1114566489
- Herbert Fröhlich *Theory of Dielectrics: Dielectric Constant and Dielectric Loss* (Clarendon Press, 1949, 1958)
- Herbert Fröhlich and F. Kremer *Coherent Excitations in Biological Systems* (Springer-Verlag, 1983)
- Herbert Fröhlich, editor *Biological Coherence and Response to External Stimuli* (Springer, 1988) ISBN 978-0387187396

Bibliography

- Terence W. Barrett and Herbert A. Pohl *Energy Transfer Dynamics: Studies and Essays in Honor of Herbert Frohlich on His Eightieth Birthday* (Springer-Verlag, 1987) ISBN 978-3540175025

- GJ Hyland and Peter Rowlands (editors) *Herbert Frohlich FRS: A Physicist Ahead of his Time.* (University of Liverpool, 2006, 2nd edition 2008.) ISBN 978-0-906370-57-5

See also

- Quantum mind

External links

- Fröhlich Biography [7] – International Institute of Biophysics
- NCUACS Fröhlich archive [8]
- Liverpool Univ bio [9]
- Fröhlich's math genealogy [10]

References

[1] Fröhlich (http://genealogy.math.ndsu.nodak.edu/html/id.phtml?id=66698) – Mathematics Genealogy Project. Dr. phil. Ludwig-Maximilians-Universität München. 1930 Dissertation title: *Zum Photoeffekt an Metallen*. Advisor: Arnold Sommerfeld.

[2] Fröhlich Biography (http://www.lifescientists.de/conference/herbertfroehlich.htm) – International Institute of Biophysics

[3] Fröhlich (http://www.physics.purdue.edu/alumni/hondegree/frohlich.shtml) – Purdue University

[4] Fröhlich (http://www.liv.ac.uk/physics/latest_news/news_07_04_06.html) – University of Liverpool

[5] Fröhlich Coherence (http://www.nonlocal.com/hbar/frohlich.html)

[6] Fröhlich Coherence (http://www.i-sis.org.uk/prague.php) – Institute of Science in Society

[7] http://www.lifescientists.de/conference/herbertfroehlich.htm

[8] http://www.bath.ac.uk/ncuacs/AHRC.htm

[9] http://www.liv.ac.uk/physics/latest_news/news_07_04_06.html

[10] http://genealogy.math.ndsu.nodak.edu/id.php?id=66698

Mathematical Biophysics

Theoretical physics

Theoretical physics is a branch of physics which employs mathematical models and abstractions of physics in an attempt to explain natural phenomena. Its central core is mathematical physics,[1] though other conceptual techniques are also used. The goal is to rationalize, explain and predict physical phenomena. The advancement of science depends in general on the interplay between experimental studies and theory. In some cases, theoretical physics adheres to standards of mathematical rigor while giving little weight to experiments and observations. For example, while developing special relativity, Albert Einstein was concerned with the Lorentz transformation which left Maxwell's equations invariant, but was apparently uninterested in the Michelson-Morley experiment on Earth's drift through a luminiferous ether. On the other hand, Einstein was awarded the Nobel Prize for explaining the photoelectric effect, previously an experimental result lacking a theoretical formulation.

Overview

A **physical theory** is a model of physical events. It is judged by the extent to which its predictions agree with empirical observations. The quality of a physical theory is also judged on its ability to make new predictions which can be verified by new observations. A physical theory differs from a mathematical theorem in that while both are based on some form of axioms, judgment of mathematical applicability is not based on agreement with any experimental results.

> $\mathrm{Ricci} = k\,g$
>
> *The equations for an Einstein manifold, used in general relativity to describe the curvature of spacetime*

A physical theory involves one or more relationships between various measurable quantities. Archimedes realized that a ship floats by displacing its mass of water, Pythagoras understood the relation between the length of a vibrating string and the musical tone it produces, and how to calculate the length of a rectangle's diagonal. Other examples include entropy as a measure of the uncertainty regarding the positions and motions of unseen particles and the quantum mechanical idea that (action and) energy are not continuously variable.

Sometimes the vision provided by pure mathematical systems can provide clues to how a physical system might be modeled; e.g., the notion, due to Riemann and others, that space itself might be curved.

Theoretical advances may consist in setting aside old, incorrect paradigms (e.g., Burning consists of evolving phlogiston, or Astronomical bodies revolve around the Earth) or may be an alternative model that provides answers that are more accurate or that can be more widely applied.

Physical theories become accepted if they are able to make correct predictions and no (or few) incorrect ones. The theory should have, at least as a secondary objective, a certain economy and elegance (compare to mathematical beauty), a notion sometimes called "Occam's razor" after the 13th-century English philosopher William of Occam (or Ockham), in which the simpler of two theories that describe the same matter just as adequately is preferred. (But conceptual simplicity may mean mathematical complexity.) They are also more likely to be accepted if they connect a wide range of phenomena. Testing the consequences of a theory is part of the scientific method.

Physical theories can be grouped into three categories: *mainstream theories*, *proposed theories* and *fringe theories*.

History

Theoretical physics began at least 2,300 years ago, under the pre-Socratic Greek philosophers, and continued by Plato; and Aristotle, whose views held sway for a millennium. In medieval times, during the rise of the universities, the only acknowledged intellectual disciplines were theology, mathematics, medicine, and law. As the concepts of matter, energy, space, time and causality slowly began to acquire the form we know today, other sciences spun off from the rubric of natural philosophy. During the Middle Ages and Renaissance, the concept of experimental science, the counterpoint to theory, began with scholars such as Ibn al-Haytham and Francis Bacon. The modern era of theory began perhaps with the Copernican paradigm shift in astronomy, soon followed by Johannes Kepler's expressions for planetary orbits, which summarized the meticulous observations of Tycho Brahe.

The great push toward the modern concept of explanation started with Galileo, one of the few physicists who was both a consummate theoretician and a great experimentalist. The analytic geometry and mechanics of Descartes were incorporated into the calculus and mechanics of Isaac Newton, another theoretician/experimentalist of the highest order. Joseph-Louis Lagrange, Leonhard Euler and William Rowan Hamilton would extend the theory of classical mechanics considerably. Each of these individuals picked up the interactive intertwining of mathematics and physics begun two millennia earlier by Pythagoras.

Among the great conceptual achievements of the 19th and 20th centuries were the consolidation of the idea of energy by the inclusion of heat, then electricity and magnetism and light, and finally mass. The laws of thermodynamics, and especially the introduction of the singular concept of entropy began to provide a macroscopic explanation for the properties of matter.

The pillars of modern physics, and perhaps the most revolutionary theories in the history of physics, have been relativity theory and quantum mechanics. Newtonian mechanics was subsumed under special relativity and Newton's gravity was given a kinematic explanation by general relativity. Quantum mechanics led to an understanding of blackbody radiation and of anomalies in the specific heats of solids — and finally to an understanding of the internal structures of atoms and molecules.

All of these achievements depended on the theoretical physics as a moving force both to suggest experiments and to consolidate results — often by ingenious application of existing mathematics, or, as in the case of Descartes and Newton (with Leibniz), by inventing new mathematics. Fourier's studies of heat conduction led to a new branch of mathematics: infinite, orthogonal series.

Modern theoretical physics attempts to unify theories and explain phenomena in further attempts to understand the Universe, from the cosmological to the elementary particle scale. Where experimentation cannot be done, theoretical physics still tries to advance through the use of mathematical models. Some of their most prominent and well thought out advancements in this field include:

Prominent theoretical physicists

Famous *theoretical physicists* include

- Christiaan Huyghens (1629−1695)
- Isaac Newton (1643−1727)
- Leonhard Euler (1707−1783)
- Joseph Louis Lagrange (1736−1813)
- Pierre-Simon Laplace (1749−1827)
- Joseph Fourier (1768−1830)
- Nicolas Léonard Sadi Carnot (1796−1842)
- William Rowan Hamilton (1805−1865)
- Rudolf Clausius (1822−1888)
- James Clerk Maxwell (1831−1879)

- J. Willard Gibbs (1839−1903)
- Ludwig Boltzmann (1844−1906)
- Hendrik A. Lorentz (1853−1928)
- Henri Poincare (1854−1912)
- Nikola Tesla (1856−1943)
- Max Planck (1858−1947)
- Albert Einstein (1879−1955)
- Emmy Noether (1882-1935)
- Max Born (1882−1970)
- Niels Bohr (1885−1962)
- Erwin Schrödinger (1887−1961)
- Louis de Broglie (1892−1987)
- Satyendra Nath Bose (1894−1974)
- Wolfgang Pauli (1900−1958)
- Enrico Fermi (1901−1954)
- Werner Heisenberg (1901−1976)
- Paul Dirac (1902−1984)
- Eugene Wigner (1902−1995)
- Robert Oppenheimer (1904−1967)
- Sin-Itiro Tomonaga (1906−1979)
- Hideki Yukawa (1907−1981)
- John Bardeen (1908−1991)
- Lev Landau (1908−1967)
- Anatoly Vlasov (1908−1975)
- Nikolay Bogolyubov (1909−1992)
- Subrahmanyan Chandrasekhar (1910−1995)
- Richard Feynman (1918−1988)
- Julian Schwinger (1918−1994)
- Feza Gursey (1921−1992)
- Chen Ning Yang (1922−)
- Freeman Dyson (1923−)
- Gunnar Källén (1926−1968)
- Abdus Salam (1926−1996)
- Murray Gell-Mann (1929−)
- Riazuddin (1930−)
- Roger Penrose (1931−)
- George Sudarshan (1931−)
- Sheldon Glashow (1932−)
- Steven Weinberg (1933−)
- C. R. Hagen (1936−)
- Michael Berry (1941−)
- Stephen Hawking (1942−)
- Alexander Polyakov (1945−)
- Gerardus 't Hooft (1946−)
- Jacob Bekenstein (1947−)
- Bertrand Halperin (1950−)
- Robert Laughlin (1950−)

- Edward Witten (1951–)

Mainstream theories

Mainstream theories (sometimes referred to as *central theories*) are the body of knowledge of both factual and scientific views and possess a usual scientific quality of the tests of repeatability, consistency with existing well-established science and experimentation. There do exist mainstream theories that are generally accepted theories based solely upon their effects explaining a wide variety of data, although the detection, explanation and possible composition are subjects of debate.

Examples

- Black hole thermodynamics
- Classical mechanics
- Condensed matter physics
- Conservation of energy
- Dark Energy
- Dark matter
- Dynamics
- Electromagnetism
- Field theory
- Fluid dynamics
- General relativity
- Molecular modeling
- Particle physics
- Physical cosmology
- Quantum chromodynamics
- Quantum computers
- Quantum electrochemistry
- Quantum electrodynamics
- Quantum field theory
- Quantum information theory
- Quantum mechanics
- Solid mechanics
- Solid state physics or Condensed Matter Physics and the electronic structure of materials
- Special relativity
- Standard Model
- Statistical mechanics
- Thermodynamics

Proposed theories

The **proposed theories** of physics are usually relatively new theories which deal with the study of physics which include scientific approaches, means for determining the validity of models and new types of reasoning used to arrive at the theory. However, some proposed theories include theories that have been around for decades and have eluded methods of discovery and testing. Proposed theories can include fringe theories in the process of becoming established (and, sometimes, gaining wider acceptance). Proposed theories usually have not been tested.

Examples

- Causal Sets
- Dark energy or Einstein's Cosmological Constant
- Einstein-Rosen Bridge
- Emergence
- Grand unification theory
- Loop quantum gravity
- M-theory
- String theory
- Supersymmetry
- Theory of everything

Fringe theories

Fringe theories include any new area of scientific endeavor in the process of becoming established and some proposed theories. It can include speculative sciences. This includes physics fields and physical theories presented in accordance with known evidence, and a body of associated predictions have been made according to that theory.

Some fringe theories go on to become a widely accepted part of physics. Other fringe theories end up being disproven. Some fringe theories are a form of protoscience and others are a form of pseudoscience. The falsification of the original theory sometimes leads to reformulation of the theory.

Examples

- Dynamic theory of gravity
- Grand unification theory
- Luminiferous aether
- Scalar field theory (pseudoscience)
- Orgone
- Biefeld Brown Electrogravity

Thought experiments vs real experiments

"Thought" experiments are situations created in ones mind, asking a question akin to "Suppose you are in this situation. Assuming such is true, what would follow?". They are usually created to investigate phenomena that are not readily experienced in every-day situations. Famous examples of such thought experiments are Schrodinger's cat, the EPR thought experiment, simple illustrations of time dilation, and so on. These usually lead to real experiments designed to verify that the conclusion (and therefore the assumptions) of the thought experiments are correct. The EPR thought experiment lead to the Bell inequalities, which were then tested to various degrees of rigor, leading to the acceptance of the current formulation of quantum mechanics and probabilism as a working hypotheses.

See also

- Experimental physics
- List of theoretical physicists

Further reading

- Landau, L. D.; Lifshitz, E. M. (1976). *Course of Theoretical Physics*. Butterworth-Heinemann. ISBN 0-7506-2896-0.
- Morse, Philip; Feshbach, Herman (2005). *Methods of Theoretical Physics*. Feshbach Publishing. ISBN 0-9762021-2-3.

External links

- Timeline of Theoretical Physics [2]
- MIT Center for Theoretical Physics [3]
- Electronic Journal of Theoretical Physics (EJTP) [4]
- How to Become a Theoretical Physicist by a Nobel Laureate [5]
- Theory of longitudinal and transversal angular momentums [6]

References

[1] Sometimes *mathematical physics* and *theoretical physics* are used synonymously to refer to the latter.
[2] http://superstringtheory.com/history/history3.html
[3] http://ctp.lns.mit.edu/index.html
[4] http://www.ejtp.com
[5] http://www.phys.uu.nl/~thooft/theorist.html
[6] http://www.odomann.com

Theoretical Biophysics

Biophysics is an interdisciplinary science that uses the methods of physics and physical chemistry to study biological systems.[1] Studies included under the branches of biophysics span all levels of biological organization, from the molecular scale to whole organisms and ecosystems. Biophysical research shares significant overlap with biochemistry, nanotechnology, bioengineering, agrophysics and systems biology.

Molecular biophysics typically addresses biological questions that are similar to those in biochemistry and molecular biology, but the questions are approached quantitatively. Scientists in this field conduct research concerned with understanding the interactions between the various systems of a cell, including the interactions between DNA, RNA and protein biosynthesis, as well as how these interactions are regulated. A great variety of techniques are used to answer these questions.

Fluorescent imaging techniques, as well as electron microscopy, x-ray crystallography, NMR spectroscopy and atomic force microscopy (AFM) are often used to visualize structures of biological significance. Conformational change in structure can be measured using techniques such as dual polarisation interferometry and circular dichroism. Direct manipulation of molecules using optical tweezers or AFM can also be used to monitor biological events where forces and distances are at the nanoscale. Molecular biophysicists often consider complex biological events as systems of interacting units which can be understood through statistical mechanics, thermodynamics and chemical kinetics. By drawing knowledge and experimental techniques from a wide variety of disciplines, biophysicists are often able to directly observe, model or even manipulate the structures and interactions of individual molecules or complexes of molecules.

In addition to traditional (i.e. molecular and cellular) biophysical topics like structural biology or enzyme kinetics, modern biophysics encompasses an extraordinarily broad range of research. It is becoming increasingly common for biophysicists to apply the models and experimental techniques derived from physics, as well as mathematics and statistics, to larger systems such as tissues, organs, populations and ecosystems.

Focus as a subfield

Biophysics often does not have university-level departments of its own, but has presence as groups across departments within the fields of molecular biology, biochemistry, chemistry, computer science, mathematics, medicine, pharmacology, physiology, physics, and neuroscience. What follows is a list of examples of how each department applies its efforts toward the study of biophysics. This list is hardly all inclusive. Nor does each subject of study belong exclusively to any particular department. Each academic institution makes its own rules and there is much overlap between departments.

- Biology and molecular biology - Almost all forms of biophysics efforts are included in some biology department somewhere. To include some: gene regulation, single protein dynamics, bioenergetics, patch clamping, biomechanics.
- Structural biology - Ångstrom-resolution structures of proteins, nucleic acids, lipids, carbohydrates, and complexes thereof.
- Biochemistry and chemistry - biomolecular structure, SIRNA, nucleic acid structure, structure-activity relationships.
- Computer science - Neural networks, biomolecular and drug databases.
- Computational chemistry - molecular dynamics simulation, molecular docking, quantum chemistry
- Bioinformatics - sequence alignment, structural alignment, protein structure prediction
- Mathematics - graph/network theory, population modeling, dynamical systems, phylogenetics.
- Medicine and neuroscience - tackling neural networks experimentally (brain slicing) as well as theoretically (computer models), membrane permitivity, gene therapy, understanding tumors.

- Pharmacology and physiology - channel biology, biomolecular interactions, cellular membranes, polyketides.
- Physics - biomolecular free energy, stochastic processes, covering dynamics.
- Quantum Biophysics involves the quantum information of processing of coherent states, entanglement between coherent protons and transcriptase components and replication of decohered isomers to yield time-dependent base substitutions. These studies imply applicatons in quantum computing.
- Agronomy Agriculture

Many biophysical techniques are unique to this field. Research efforts in biophysics are often initiated by scientists who were traditional physicists, chemists, and biologists by training.

See also

- List of biophysics topics
- List of biophysicists
- Biophysical chemistry
- Medical biophysics
- Membrane biophysics
- Molecular biophysics
- Important publications in biophysics

References

- Perutz MF (1962). *Proteins and Nucleic Acids: Structure and Function*. Amsterdam: Elsevier. ASIN B000TS8P4G [2].
- Perutz MF (1969). "The haemoglobin molecule". *Proceedings of the Royal Society of London. Series B* **173** (31): 113−40. PMID 4389425
- Dogonadze RR, Urushadze ZD (1971). "Semi-Classical Method of Calculation of Rates of Chemical Reactions Proceeding in Polar Liquids". *J Electroanal Chem* **32**: 235−245.
- Volkenshtein M.V., Dogonadze R.R., Madumarov A.K., Urushadze Z.D. and Kharkats Yu.I. Theory of Enzyme Catalysis.- *Molekuliarnaya Biologia* (Moscow), 6, 1972, pp. 431-439 (In Russian, English summary)
- Rodney M. J. Cotterill (2002). *Biophysics : An Introduction*. Wiley. ISBN 978-0471485384.
- Sneppen K, Zocchi G (2005-10-17). *Physics in Molecular Biology* (1 ed.). Cambridge University Press. ISBN 0-521-84419-3.
- Glaser, Roland (2004-11-23). *Biophysics: An Introduction* (Corrected ed.). Springer. ISBN 3-540-67088-2.
- Hobbie RK, Roth BJ (2006). *Intermediate Physics for Medicine and Biology* [3] (4th ed.). Springer. ISBN 978-0387309422.
- Cooper WG (2009). "Evidence for transcriptase quantum processing implies entanglement and decoherence of superposition proton states". *BioSystems* **97**: 73−89.
- Cooper WG (2009). "Necessity of quantum coherence to account for the spectrum of time-dependent mutations exhibited by bacteriophage T4". *Biochem. Genet.* **47**: 892.

External links

- Biophysical Society [4]
- Educational Resources from Biophysical Society [5]
- The European Biophysical Societies Association [6]
- The Wellcome Trust Physiome Project [7] - Links
- Nasif Nahle, Biophysics [8]

References

[1] Careers in Biophysics brochure, Biophysical Society https://www.biophysics.org/Portals/1/PDFs/Career%20Center/
    Careers%20In%20Biophysics.pdf

[2] http://www.amazon.com/dp/B000TS8P4G

[3] http://personalwebs.oakland.edu/~roth/hobbie.htm

[4] http://www.biophysics.org/

[5] http://www.biophysics.org/education/resources.htm

[6] http://www.ebsa.org/

[7] http://www.physiome.ox.ac.uk/

[8] http://biocab.org/Biophysics.html

Mathematical Biophysics

Mathematical and theoretical biology is an interdisciplinary academic research field with a range of applications in biology, medicine and biotechnology.[1] The field may be referred to as **mathematical biology** or **biomathematics** to stress the mathematical side, or as **theoretical biology** to stress the biological side.[2] It includes at least four major subfields: *biological mathematical modeling*, *relational biology/complex systems biology (CSB)*, *bioinformatics* and *computational biomodeling/biocomputing*.

Mathematical biology aims at the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools. It has both theoretical and practical applications in biological, biomedical and biotechnology research. For example, in cell biology, protein interactions are often represented as "cartoon" models, which, although easy to visualize, do not accurately describe the systems studied. In order to do this, precise mathematical models are required. By describing the systems in a quantitative manner, their behavior can be better simulated, and hence properties can be predicted that might not be evident to the experimenter.

Importance

Applying mathematics to biology has a long history, but only recently has there been an explosion of interest in the field. Some reasons for this include:

- the explosion of data-rich information sets, due to the genomics revolution, which are difficult to understand without the use of analytical tools,
- recent development of mathematical tools such as chaos theory to help understand complex, nonlinear mechanisms in biology,
- an increase in computing power which enables calculations and simulations to be performed that were not previously possible, and
- an increasing interest in in silico experimentation due to ethical considerations, risk, unreliability and other complications involved in human and animal research.

Areas of research

Several areas of specialized research in mathematical and theoretical biology[3] [4] [5] [6] [7] as well as external links to related projects in various universities are concisely presented in the following subsections, including also a large number of appropriate validating references from a list of several thousands of published authors contributing to this field. Many of the included examples are characterised by highly complex, nonlinear, and supercomplex mechanisms, as it is being increasingly recognised that the result of such interactions may only be understood through a combination of mathematical, logical, physical/chemical, molecular and computational models. Due to the wide diversity of specific knowledge involved, biomathematical research is often done in collaboration between mathematicians, biomathematicians, theoretical biologists, physicists, biophysicists, biochemists, bioengineers, engineers, biologists, physiologists, research physicians, biomedical researchers, oncologists, molecular biologists, geneticists, embryologists, zoologists, chemists, etc.

Computer models and automata theory

A monograph on this topic summarizes an extensive amount of published research in this area up to 1987,[8] including subsections in the following areas: computer modeling in biology and medicine, arterial system models, neuron models, biochemical and oscillation networks, quantum automata [9], quantum computers in molecular biology and genetics, cancer modelling, neural nets, genetic networks, abstract relational biology, metabolic-replication systems, category theory[10] applications in biology and medicine,[11] automata theory,cellular automata, tessallation models[12] [13] and complete self-reproduction [14], chaotic systems in organisms, relational biology and organismic theories.[15] [16] This published report also includes 390 references to peer-reviewed articles by a large number of authors.[3] [17] [18]

Modeling cell and molecular biology

This area has received a boost due to the growing importance of molecular biology.[6]

- Mechanics of biological tissues[19]
- Theoretical enzymology and enzyme kinetics
- Cancer modelling and simulation[20] [21]
- Modelling the movement of interacting cell populations[22]
- Mathematical modelling of scar tissue formation[23]
- Mathematical modelling of intracellular dynamics[24]
- Mathematical modelling of the cell cycle[25]

Modelling physiological systems

- Modelling of arterial disease [26]
- Multi-scale modelling of the heart [27]

Molecular set theory

Molecular set theory was introduced by Anthony Bartholomay, and its applications were developed in mathematical biology and especially in Mathematical Medicine.[28] Molecular set theory (MST) is a mathematical formulation of the wide-sense chemical kinetics of biomolecular reactions in terms of sets of molecules and their chemical transformations represented by set-theoretical mappings between molecular sets. In a more general sense, MST is the theory of molecular categories defined as categories of molecular sets and their chemical transformations represented as set-theoretical mappings of molecular sets. The theory has also contributed to biostatistics and the formulation of clinical biochemistry problems in mathematical formulations of pathological, biochemical changes of interest to Physiology, Clinical Biochemistry and Medicine.[28] [29]

Population dynamics

Population dynamics has traditionally been the dominant field of mathematical biology. Work in this area dates back to the 19th century. The Lotka–Volterra predator-prey equations are a famous example. In the past 30 years, population dynamics has been complemented by evolutionary game theory, developed first by John Maynard Smith. Under these dynamics, evolutionary biology concepts may take a deterministic mathematical form. Population dynamics overlap with another active area of research in mathematical biology: mathematical epidemiology, the study of infectious disease affecting populations. Various models of the spread of infections have been proposed and analyzed, and provide important results that may be applied to health policy decisions.

Mathematical methods

A model of a biological system is converted into a system of equations, although the word 'model' is often used synonymously with the system of corresponding equations. The solution of the equations, by either analytical or numerical means, describes how the biological system behaves either over time or at equilibrium. There are many different types of equations and the type of behavior that can occur is dependent on both the model and the equations used. The model often makes assumptions about the system. The equations may also make assumptions about the nature of what may occur.

Mathematical biophysics

The earlier stages of mathematical biology were dominated by mathematical biophysics, described as the application of mathematics in biophysics, often involving specific physical/mathematical models of biosystems and their components or compartments.

The following is a list of mathematical descriptions and their assumptions.

Deterministic processes (dynamical systems)

A fixed mapping between an initial state and a final state. Starting from an initial condition and moving forward in time, a deterministic process will always generate the same trajectory and no two trajectories cross in state space.

- Difference equations – discrete time, continuous state space.
- Ordinary differential equations – continuous time, continuous state space, no spatial derivatives. *See also:* Numerical ordinary differential equations.
- Partial differential equations – continuous time, continuous state space, spatial derivatives. *See also:* Numerical partial differential equations.
- Maps – discrete time, continuous state space.

Stochastic processes (random dynamical systems)

A random mapping between an initial state and a final state, making the state of the system a random variable with a corresponding probability distribution.

- Non-Markovian processes – generalized master equation – continuous time with memory of past events, discrete state space, waiting times of events (or transitions between states) discretely occur and have a generalized probability distribution.
- Jump Markov process – master equation – continuous time with no memory of past events, discrete state space, waiting times between events discretely occur and are exponentially distributed. *See also:* Monte Carlo method for numerical simulation methods, specifically continuous-time Monte Carlo which is also called kinetic Monte Carlo or the stochastic simulation algorithm.
- Continuous Markov process – stochastic differential equations or a Fokker-Planck equation – continuous time, continuous state space, events occur continuously according to a random Wiener process.

Spatial modelling

One classic work in this area is Alan Turing's paper on morphogenesis entitled *The Chemical Basis of Morphogenesis*, published in 1952 in the Philosophical Transactions of the Royal Society.

- Travelling waves in a wound-healing assay[30]
- Swarming behaviour[31]
- A mechanochemical theory of morphogenesis[32]
- Biological pattern formation[33]
- Spatial distribution modeling using plot samples[34]

Phylogenetics

Phylogenetics is an area that deals with the reconstruction and analysis of phylogenetic (evolutionary) trees and networks based on inherited characteristics[35]

Model example: the cell cycle

The eukaryotic cell cycle is very complex and is one of the most studied topics, since its misregulation leads to cancers. It is possibly a good example of a mathematical model as it deals with simple calculus but gives valid results. Two research groups [36] [37] have produced several models of the cell cycle simulating several organisms. They have recently produced a generic eukaryotic cell cycle model which can represent a particular eukaryote depending on the values of the parameters, demonstrating that the idiosyncrasies of the individual cell cycles are due to different protein concentrations and affinities, while the underlying mechanisms are conserved (Csikasz-Nagy et al., 2006).

By means of a system of ordinary differential equations these models show the change in time (dynamical system) of the protein inside a single typical cell; this type of model is called a deterministic process (whereas a model describing a statistical distribution of protein concentrations in a population of cells is called a stochastic process).

To obtain these equations an iterative series of steps must be done: first the several models and observations are combined to form a consensus diagram and the appropriate kinetic laws are chosen to write the differential equations, such as rate kinetics for stoichiometric reactions, Michaelis-Menten kinetics for enzyme substrate reactions and Goldbeter–Koshland kinetics for ultrasensitive transcription factors, afterwards the parameters of the equations (rate constants, enzyme efficiency coefficients and Michealis constants) must be fitted to match observations; when they cannot be fitted the kinetic equation is revised and when that is not possible the wiring diagram is modified. The parameters are fitted and validated using observations of both wild type and mutants, such as protein half-life and cell size.

In order to fit the parameters the differential equations need to be studied. This can be done either by simulation or by analysis.

In a simulation, given a starting vector (list of the values of the variables), the progression of the system is calculated by solving the equations at each time-frame in small increments.

In analysis, the proprieties of the equations are used to investigate the behavior of the system depending of the values of the parameters and variables. A system of differential equations can be represented as a vector field, where each vector described the change (in concentration of two or more protein) determining where and how fast the trajectory (simulation) is heading. Vector fields can have several special points: a

stable point, called a sink, that attracts in all directions (forcing the concentrations to be at a certain value), an unstable point, either a source or a saddle point which repels (forcing the concentrations to change away from a certain value), and a limit cycle, a closed trajectory towards which several trajectories spiral towards (making the concentrations oscillate).

A better representation which can handle the large number of variables and parameters is called a bifurcation diagram(Bifurcation theory): the presence of these special steady-state points at certain values of a parameter (e.g. mass) is represented by a point and once the parameter passes a certain value, a qualitative change occurs, called a bifurcation, in which the nature of the space changes, with profound consequences for the protein concentrations: the cell cycle has phases (partially corresponding to G1 and G2) in which mass, via a stable point, controls cyclin levels, and phases (S and M phases) in which the concentrations change independently, but once the phase has changed at a bifurcation event (Cell cycle checkpoint), the system cannot go back to the previous levels since at the current mass the vector field is profoundly different and the mass cannot be reversed back through the bifurcation event, making a checkpoint irreversible. In particular the S and M checkpoints are regulated by means of special bifurcations called a Hopf bifurcation and an infinite period bifurcation.
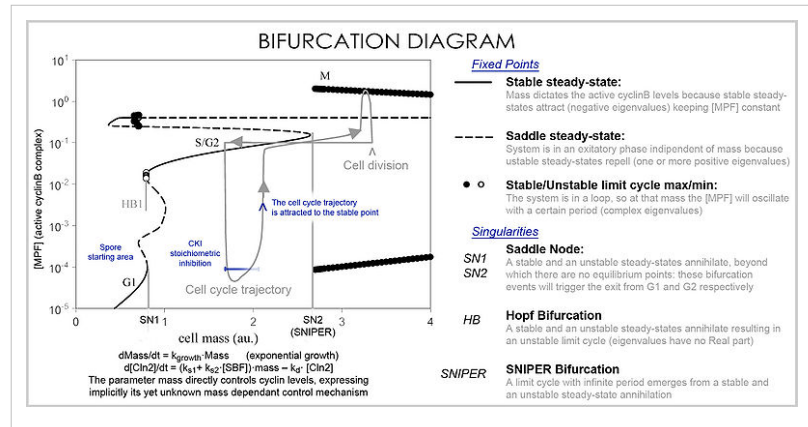
Mathematical/theoretical biologists

- Nicolas Rashevsky
- Pere Alberch
- Anthony F. Bartholomay
- J. T. Bonner
- Jack Cowan
- Walter M. Elsasser
- Claus Emmeche
- Andree Ehresmann
- Marc Feldman
- Ronald A. Fisher
- Brian Goodwin
- Bryan Grenfell
- J. B. S. Haldane
- William D. Hamilton
- Lionel G. Harrison
- Michael Hassell
- Sven Erik Jørgensen
- George Karreman

- Stuart Kauffman
- Kalevi Kull
- Herbert D. Landahl
- Russ Lande
- Richard Lewontin
- Philip K. Maini
- Humberto Maturana
- Jagannath Mazumdar
- Robert May
- John Maynard Smith
- Gerd B. Müller
- James D. Murray
- Robert V. ONeill
- Howard Pattee
- George R. Price
- Erik Rauch
- Ronald Brown (mathematician)
- Johannes Reinke
- Robert Rosen
- Lee A. Segel
- Santiago Schnell
- William D. Stone
- George Sugihara
- René Thom
- Jakob von Uexküll
- Robert Ulanowicz
- Francisco Varela
- C. H. Waddington
- Arthur Winfree
- Lewis Wolpert
- Sewall Wright
- Christopher Zeeman

Mathematical, theoretical and computational biophysicists

- Nicolas Rashevsky-(Mathematical Biophysics, Mathematical Biology and Mathematical sociology)
- Ludwig von Bertalanffy
- Francis Crick-(Theoretical Biophysics)
- Manfred Eigen-(Quantum Biochemistry)
- Walter Elsasser-(Theoretical Biology/ Theoretical Biophysics)
- Herbert Frohlich, FRS
- Francois Jacob
- Martin Karplus
- George Karreman-(Mathematical Biology and Quantum Biology)
- Herbert D. Landahl-(Mathematical Biology)
- Ilya, Viscount Prigogine
- SirJohn Randall-(Theoretical and Experimental Biophysics)
- James D. Murray

- Bernard Pullman-(Quantum Biochemistry)
- Alberte Pullman-(Quantum Biochemistry)
- Erwin Schrodinger-(Quantum theory and Quantum Biochemistry)
- Klaus Schulten
- Peter Schuster
- Zeno Simon-(Theoretical Biology)
- D'Arcy Thompson-(Mathematical Biology)
- Murray Gell-Mann-(Quantum theory and Theoretical Biophysics)

See also

- Abstract relational biology [38][39] [40]
- Biocybernetics
- Bioinformatics
- Biologically inspired computing
- Biostatistics
- Cellular automata[3]
- Coalescent theory
- Complex systems biology[41] [3] [42]
- Computational biology
- Digital morphogenesis
- Dynamical systems in biology[3] [42] [43] [44] [45] [46]
- Epidemiology
- Evolution theories and Population Genetics

  - Population genetics models
  - Molecular evolution theories
- Ewens's sampling formula
- Excitable medium
- Mathematical models

  - Molecular modelling
  - Molecular modelling on GPU
  - Software for molecular modeling
  - Metabolic-replication systems[47]
  - Models of Growth and Form
  - Neighbour-sensing model
- Morphometrics
- Organismic systems (OS) [48][49]
- Organismic supercategories [48][42] [50]
- Population dynamics of fisheries
- Protein folding, also blue Gene and folding@home
- Quantum computers
- Quantum genetics
- Relational biology[51]
- Self-reproduction[52] (also called self-replication in a more general context).
- Computational gene models
- Systems biology[53]
- Theoretical biology[54]

- Topological models of morphogenesis
  - DNA topology
  - DNA sequencing theory

    For use of basic arithmetics in biology, see relevant topic, such as Serial dilution.
- Biographies
  - Charles Darwin
  - D'Arcy Thompson
  - Joseph Fourier
  - Charles S. Peskin
  - Nicolas Rashevsky [55]
  - Robert Rosen
  - Rosalind Franklin
  - Francis Crick
  - René Thom
  - Vito Volterra

Mathematical and Theoretical Biology Societies and Institutes

- Division of Mathematical Biology at NIMR
- Society for Mathematical Biology
- European Society for Mathematical and Theoretical Biology

References

- Nicolas Rashevsky. (1938)., *Mathematical Biophysics*. Chicago: University of Chicago Press.
- Robert Rosen, Dynamical system theory in biology. New York, Wiley-Interscience (1970) ISBN 0471735507 [56]
- Israel, G., 2005, "Book on mathematical biology" in Grattan-Guinness, I., ed., *Landmark Writings in Western Mathematics*. Elsevier: 936-44.
- Israel G (1988). "On the contribution of Volterra and Lotka to the development of modern biomathematics". *History and Philosophy of the Life Sciences* **10** (1): 37–49. PMID 3045853 [57].
- Scudo FM (March 1971). "Vito Volterra and theoretical ecology". *Theoretical Population Biology* **2** (1): 1–23. doi:10.1016/0040-5809(71)90002-5 [58]. PMID 4950157 [59].
- S.H. Strogatz, *Nonlinear dynamics and Chaos: Applications to Physics, Biology, Chemistry, and Engineering.* Perseus, 2001, ISBN 0-7382-0453-6
- N.G. van Kampen, *Stochastic Processes in Physics and Chemistry*, North Holland., 3rd ed. 2001, ISBN 0-444-89349-0
- I. C. Baianu., Computer Models and Automata Theory in Biology and Medicine., *Monograph*, Ch.11 in M. Witten (Editor), *Mathematical Models in Medicine*, vol. **7**., Vol. **7**: 1513-1577 (1987),Pergamon Press:New York, (updated by Hsiao Chen Lin in 2004[60] ,[61] ,[62] ISBN 0080363776 [63] .
- P.G. Drazin, *Nonlinear systems*. C.U.P., 1992. ISBN 0-521-40668-4
- L. Edelstein-Keshet, *Mathematical Models in Biology*. SIAM, 2004. ISBN 0-07-554950-6
- G. Forgacs and S. A. Newman, *Biological Physics of the Developing Embryo*. C.U.P., 2005. ISBN 0-521-78337-2
- A. Goldbeter, *Biochemical oscillations and cellular rhythms*. C.U.P., 1996. ISBN 0-521-59946-6
- L.G. Harrison, *Kinetic theory of living pattern*. C.U.P., 1993. ISBN 0-521-30691-4
- F. Hoppensteadt, *Mathematical theories of populations: demographics, genetics and epidemics*. SIAM, Philadelphia, 1975 (reprinted 1993). ISBN 0-89871-017-0
- D.W. Jordan and P. Smith, *Nonlinear ordinary differential equations*, 2nd ed. O.U.P., 1987. ISBN 0-19-856562-3

- J.D. Murray, *Mathematical Biology*. Springer-Verlag, 3rd ed. in 2 vols.: *Mathematical Biology: I. An Introduction*, 2002 ISBN 0-387-95223-3; *Mathematical Biology: II. Spatial Models and Biomedical Applications*, 2003 ISBN 0-387-95228-4.
- E. Renshaw, *Modelling biological populations in space and time*. C.U.P., 1991. ISBN 0-521-44855-7
- S.I. Rubinow, *Introduction to mathematical biology*. John Wiley, 1975. ISBN 0-471-74446-8
- L.A. Segel, *Modeling dynamic phenomena in molecular and cellular biology*. C.U.P., 1984. ISBN 0-521-27477-X
- L. Preziosi, *Cancer Modelling and Simulation*. Chapman Hall/CRC Press, 2003. ISBN 1-58488-361-8.

Lists of references

- A general list of Theoretical biology/Mathematical biology references, including an updated list of actively contributing authors[54] .
- A list of references for applications of category theory in relational biology.[64]
- An updated list of publications of theoretical biologist Robert Rosen[65]

External

- *The Society for Mathematical Biology* [66]
- F. Hoppensteadt, *Getting Started in Mathematical Biology* [67]. Notices of American Mathematical Society, Sept. 1995.
- M. C. Reed, *Why Is Mathematical Biology So Hard?* [68] Notices of American Mathematical Society, March, 2004.
- R. M. May, *Uses and Abuses of Mathematics in Biology* [69]. Science, February 6, 2004.
- J. D. Murray, *How the leopard gets its spots?* [70] Scientific American, 258(3): 80-87, 1988.
- S. Schnell, R. Grima, P. K. Maini, *Multiscale Modeling in Biology* [71], American Scientist, Vol 95, pages 134-142, March-April 2007.
- Chen KC et al. Integrative analysis of cell cycle control in budding yeast. Mol Biol Cell. 2004 Aug;15(8):3841-62.
- Csikász-Nagy A et al. Analysis of a generic model of eukaryotic cell-cycle regulation. Biophys J. 2006 Jun 15;90(12):4361-79.
- Fuss H, et al. Mathematical models of cell cycle regulation. Brief Bioinform. 2005 Jun;6(2):163-77.
- Lovrics A et al. *Time scale and dimension analysis of a budding yeast cell cycle model.* [72] BMC Bioinform. 2006 Nov 9;7:494.

External links

- The Society for Mathematical Biology [73]
- Theoretical and mathematical biology website [74]
- Complexity Discussion Group [75]
- UCLA Biocybernetics Laboratory [76]
- TUCS Computational Biomodelling Laboratory [77]
- Nagoya University Division of Biomodeling [78]
- Technische Universiteit Biomodeling and Informatics [79]
- BioCybernetics Wiki, a vertical wiki on biomedical cybernetics and systems biology [80]
- Bulletin of Mathematical Biology [81]
- European Society for Mathematical and Theoretical Biology [82]
- Journal of Mathematical Biology [83]
- Biomathematics Research Centre at University of Canterbury [84]
- Centre for Mathematical Biology at Oxford University [85]

- Mathematical Biology at the National Institute for Medical Research [86]
- Institute for Medical BioMathematics [87]
- *Mathematical Biology Systems of Differential Equations* [88] from EqWorld: The World of Mathematical Equations
- Systems Biology Workbench - a set of tools for modelling biochemical networks [89]
- The Collection of Biostatistics Research Archive [90]
- Statistical Applications in Genetics and Molecular Biology [91]
- The International Journal of Biostatistics [92]
- Theoretical Modeling of Cellular Physiology at Ecole Normale Superieure, Paris [93]

References

[1] Mathematical and Theoretical Biology: A European Perspective (http://sciencecareers.sciencemag.org/career_development/ previous_issues/articles/2870/mathematical_and_theoretical_biology_a_european_perspective)

[2] "There is a subtle difference between mathematical biologists and theoretical biologists. Mathematical biologists tend to be employed in mathematical departments and to be a bit more interested in math inspired by biology than in the biological problems themselves, and vice versa." Careers in theoretical biology (http://life.biology.mcmaster.ca/~brian/biomath/careers.theo.biol.html)

[3] Baianu, I. C.; Brown, R.; Georgescu, G.; Glazebrook, J. F. (2006). "Complex Non-linear Biodynamics in Categories, Higher Dimensional Algebra and Łukasiewicz–Moisil Topos: Transformations of Neuronal, Genetic and Neoplastic Networks". *Axiomathes* **16**: 65. doi: 10.1007/s10516-005-3973-8 (http://dx.doi.org/10.1007/s10516-005-3973-8).

[4] http://en.scientificcommons.org/1857371

[5] http://cogprints.org/3687/

[6] "Research in Mathematical Biology" (http://www.maths.gla.ac.uk/research/groups/biology/kal.htm). Maths.gla.ac.uk. . Retrieved 2008-09-10.

[7] http://acube.org/volume_23/v23-1p11-36.pdf J. R. Junck. Ten Equations that Changed Biology: Mathematics in Problem-Solving Biology Curricula, *Bioscene*, (1997), 1-36

[8] http://en.scientificcommons.org/1857371

[9] http://planetphysics.org/encyclopedia/QuantumAutomaton.html

[10] http://planetphysics.org/encyclopedia/BibliographyForCategoryTheoryAndAlgebraicTopologyApplicationsInTheoreticalPhysics.html

[11] http://planetphysics.org/encyclopedia/BibliographyForMathematicalBiophysicsAndMathematicalMedicine.html

[12] *Modern Cellular Automata* by Kendall Preston and M. J. B. Duff http://books.google.co.uk/books?id=l0_0q_e-u_UC&dq=cellular+ automata+and+tessalation&pg=PP1&ots=ciXYCF3AYm&source=citation&sig=CtaUDhisM7MalS7rZfXvp689y-8&hl=en&sa=X& oi=book_result&resnum=12&ct=result

[13] http://mathworld.wolfram.com/DualTessellation.html

[14] http://planetphysics.org/encyclopedia/ETACAxioms.html

[15] Baianu, I. C. 1987, Computer Models and Automata Theory in Biology and Medicine., in M. Witten (ed.),*Mathematical Models in Medicine*, vol. **7**., Ch.11 Pergamon Press, New York, 1513-1577. http://cogprints.org/3687/

[16] http://www.kli.ac.at/theorylab/EditedVol/W/WittenM1987a.html

[17] Currently available for download as an updated PDF: http://cogprints.ecs.soton.ac.uk/archive/00003718/01/ COMPUTER_SIMULATIONCOMPUTABILITYBIOSYSTEMSrefnew.pdf

[18] http://planetphysics.org/encyclopedia/BibliographyForMathematicalBiophysics.html

[19] http://www.maths.gla.ac.uk/~rwo/research_areas.htm

[20] Oprisan, Sorinel A.; Oprisan, Ana (2006). "A Computational Model of Oncogenesis using the Systemic Approach". *Axiomathes* **16**: 155. doi: 10.1007/s10516-005-4943-x (http://dx.doi.org/10.1007/s10516-005-4943-x).

[21] http://calvino.polito.it/~mcrtn/

[22] http://www.ma.hw.ac.uk/~jas/researchinterests/index.html

[23] http://www.ma.hw.ac.uk/~jas/researchinterests/scartissueformation.html

[24] http://www.sbi.uni-rostock.de/dokumente/p_gilles_paper.pdf

[25] http://mpf.biol.vt.edu/Research.html

[26] http://www.maths.gla.ac.uk/~nah/research_interests.html

[27] http://www.integrativebiology.ox.ac.uk/heartmodel.html

[28] http://planetphysics.org/encyclopedia/CategoryOfMolecularSets2.html

[29] Representation of Uni-molecular and Multimolecular Biochemical Reactions in terms of Molecular Set Transformations http://planetmath. org/?op=getobj&from=objects&id=10770

[30] http://www.maths.ox.ac.uk/~maini/public/gallery/twwha.htm

[31] http://www.math.ubc.ca/people/faculty/keshet/research.html

[32] http://www.maths.ox.ac.uk/~maini/public/gallery/mctom.htm

[33] http://www.maths.ox.ac.uk/~maini/public/gallery/bpf.htm

[34] http://links.jstor.org/sici?sici=0030-1299%28199008%2958%3A3%3C257%3ASDOTMU%3E2.0.CO%3B2-S&size=LARGE& origin=JSTOR-enlargePage

[35] Charles Semple (2003), Phylogenetics (http://books.google.co.uk/books?id=uR8i2qetjSAC), Oxford University Press, ISBN 9780198509424

[36] "The JJ Tyson Lab" (http://mpf.biol.vt.edu/Tyson Lab.html). Virginia Tech. . Retrieved 2008-09-10.

[37] "The Molecular Network Dynamics Research Group" (http://cellcycle.mkt.bme.hu/). Budapest University of Technology and Economics. .

[38] http://www.kli.ac.at/theorylab/ALists/Authors_R.html

[39] http://planetphysics.org/encyclopedia/AbstractRelationalBiologyARB.html

[40] http://www.kli.ac.at/theorylab/EditedVol/M/MatsunoKDose_84.html

[41] Baianu, I. C.; Brown, R.; Glazebrook, J. F. (2007). "Categorical Ontology of Complex Spacetime Structures: the Emergence of Life and Human Consciousness". *Axiomathes* **17**: 223. doi: 10.1007/s10516-007-9011-2 (http://dx.doi.org/10.1007/s10516-007-9011-2).

[42] Băianu, I. (1970). "Organismic supercategores: II. On multistable systems". *The Bulletin of Mathematical Biophysics* **32**: 539. doi: 10.1007/BF02476770 (http://dx.doi.org/10.1007/BF02476770).

[43] Robert Rosen, *Dynamical system theory in biology.* New York, Wiley-Interscience (1970) ISBN 0471735507 http://www.worldcat.org/ oclc/101642

[44] http://cogprints.org/3674/

[45] http://cogprints.org/3829/

[46] Băianu I (December 1970). "Organismic supercategories. II. On multistable systems". *The Bulletin of Mathematical Biophysics* **32** (4): 539–61. doi: 10.1007/BF02476770 (http://dx.doi.org/10.1007/BF02476770). PMID 4327361 (http://www.ncbi.nlm.nih.gov/pubmed/ 4327361).

[47] http://planetphysics.org/encyclopedia/RSystemsCategoryOfM.html

[48] http://planetphysics.org/encyclopedia/OrganismicSetTheory.html

[49] Organisms as Super-complex Systems http://planetmath.org/?op=getobj&from=objects&id=10890

[50] http://planetmath.org/encyclopedia/SupercategoriesOfComplexSystems.html

[51] http://planetmath.org/?op=getobj&from=objects&id=10921

[52] http://planetmath.org/?method=l2h&from=objects&name=NaturalTransformationsOfOrganismicStructures&op=getobj

[53] http://www.kli.ac.at/theorylab/ALists/Authors_R.html

[54] http://www.kli.ac.at/theorylab/index.html

[55] http://planetphysics.org/encyclopedia/NicolasRashevsky.html

[56] http://www.worldcat.org/oclc/101642

[57] http://www.ncbi.nlm.nih.gov/pubmed/3045853

[58] http://dx.doi.org/10.1016%2F0040-5809%2871%2990002-5

[59] http://www.ncbi.nlm.nih.gov/pubmed/4950157

[60] http://cogprints.org/3718/1/COMPUTER_SIMULATIONCOMPUTABILITYBIOSYSTEMSrefnew.pdf

[61] http://www.springerlink.com/content/w2733h7280521632/

[62] http://www.springerlink.com/content/n8gw445012267381/

[63] http://www.bookfinder.com/dir/i/Mathematical_Models_in_Medicine/0080363776/

[64] http://planetmath.org/?method=l2h&from=objects&id=10746&op=getobj

[65] Publications list for Robert Rosen http://www.people.vcu.edu/~mikuleck/rosen.htm

[66] http://www.smb.org

[67] http://www.ams.org/notices/199509/hoppensteadt.pdf

[68] http://www.resnet.wm.edu/~jxshix/math490/reed.pdf

[69] http://www.resnet.wm.edu/~jxshix/math490/may.pdf

[70] http://www.resnet.wm.edu/~jxshix/math490/murray.doc

[71] http://eprints.maths.ox.ac.uk/567/01/224.pdf

[72] http://www.biomedcentral.com/content/pdf/1471-2105-7-494.pdf

[73] http://www.smb.org/

[74] http://www.kli.ac.at/theorylab/index.html

[75] http://www.complex.vcu.edu/

[76] http://biocyb.cs.ucla.edu/research.html

[77] http://www.tucs.fi/research/labs/combio.php

[78] http://www.agr.nagoya-u.ac.jp/english/e3senko-1.html

[79] http://www.bmi2.bmt.tue.nl/Biomedinf/

[80] http://wiki,biological-cybernetics.de

[81] http://www.springerlink.com/content/119979/

[82] http://www.esmtb.org/

[83] http://www.springerlink.com/content/100436/

[84] http://www.math.canterbury.ac.nz/bio/

[85] http://www.maths.ox.ac.uk/cmb/

[86] http://mathbio.nimr.mrc.ac.uk/

[87] http://www.imbm.org/

[88] http://eqworld.ipmnet.ru/en/solutions/syspde/spde-toc2.pdf

[89] http://sbw.kgi.edu

[90] http://www.biostatsresearch.com/repository/

[91] http://www.bepress.com/sagmb/

[92] http://www.bepress.com/ijb/

[93] http://www.biologie.ens.fr/bcsmcbs/

Bioinformatics

Bioinformatics is the application of information technology and computer science to the field of molecular biology. The term *bioinformatics* was coined by Paulien Hogeweg in 1979 for the study of informatic processes in biotic systems. Its primary use since at least the late 1980s has been in genomics and genetics, particularly in those areas of genomics involving large-scale DNA sequencing. Bioinformatics now entails the creation and advancement of databases, algorithms, computational and statistical techniques, and theory to solve formal and practical problems arising from the management and analysis of biological data. Over the past few decades rapid developments in genomic and other molecular research technologies and developments in information technologies have combined to produce a tremendous amount of information related to molecular biology. It is the name given to these mathematical and computing approaches used to glean understanding of biological processes. Common activities in bioinformatics include mapping and analyzing DNA and protein sequences, aligning different DNA and protein sequences to compare them and creating and viewing 3-D models of protein structures.

Map of the human X chromosome (from the NCBI website). Assembly of the human genome is one of the greatest achievements of bioinformatics.

The primary goal of bioinformatics is to increase our understanding of biological processes. What sets it apart from other approaches, however, is its focus on developing and applying computationally intensive techniques (e.g., pattern recognition, data mining, machine learning algorithms, and visualization) to achieve this goal. Major research efforts in the field include sequence alignment, gene finding, genome assembly, protein structure alignment, protein structure prediction, prediction of gene expression and protein-protein interactions, genome-wide association studies and the modeling of evolution.

Introduction

Bioinformatics was applied in the creation and maintenance of a database to store biological information at the beginning of the "genomic revolution", such as nucleotide and amino acid sequences. Development of this type of database involved not only design issues but the development of complex interfaces whereby researchers could both access existing data as well as submit new or revised data.

In order to study how normal cellular activities are altered in different disease states, the biological data must be combined to form a comprehensive picture of these activities. Therefore, the field of bioinformatics has evolved such that the most pressing task now involves the analysis and interpretation of various types of data, including nucleotide and amino acid sequences, protein domains, and protein structures. The actual process of analyzing and interpreting data is referred to as computational biology. Important sub-disciplines within bioinformatics and computational biology include:

a) the development and implementation of tools that enable efficient access to, and use and management of, various types of information. **b)** the development of new algorithms (mathematical formulas) and statistics with which to assess relationships among members of large data sets, such as methods to locate a gene within a sequence, predict protein structure and/or function, and cluster protein sequences into families of related sequences.

Major research areas

Sequence analysis

Since the Phage Φ-X174 was sequenced in 1977, the DNA sequences of thousands of organisms have been decoded and stored in databases. This sequence information is analyzed to determine genes that encode polypeptides (proteins), RNA genes, regulatory sequences, structural motifs, and repetitive sequences. A comparison of genes within a species or between different species can show similarities between protein functions, or relations between species (the use of molecular systematics to construct phylogenetic trees). With the growing amount of data, it long ago became impractical to analyze DNA sequences manually. Today, computer programs such as BLAST are used daily to search the genomes of thousands of organisms, containing billions of nucleotides. These programs can compensate for mutations (exchanged, deleted or inserted bases) in the DNA sequence, in order to identify sequences that are related, but not identical. A variant of this sequence alignment is used in the sequencing process itself. The so-called shotgun sequencing technique (which was used, for example, by The Institute for Genomic Research to sequence the first bacterial genome, *Haemophilus influenzae*) does not produce entire chromosomes, but instead generates the sequences of many thousands of small DNA fragments (ranging from 35 to 900 nucleotides long, depending on the sequencing technology). The ends of these fragments overlap and, when aligned properly by a genome assembly program, can be used to reconstruct the complete genome. Shotgun sequencing yields sequence data quickly, but the task of assembling the fragments can be quite complicated for larger genomes. For a genome as large as the human genome, it may take many days of CPU time on large-memory, multiprocessor computers to assemble the fragments, and the resulting assembly will usually contain numerous gaps that have to be filled in later. Shotgun sequencing is the method of choice for virtually all genomes sequenced today, and genome assembly algorithms are a critical area of bioinformatics research.

Another aspect of bioinformatics in sequence analysis is annotation, which involves computational gene finding to search for protein-coding genes, RNA genes, and other functional sequences within a genome. Not all of the nucleotides within a genome are genes. Within the genome of higher organisms, large parts of the DNA do not serve any obvious purpose. This so-called junk DNA may, however, contain unrecognized functional elements. Bioinformatics helps to bridge the gap between genome and proteome projects--for example, in the use of DNA sequences for protein identification.

Genome annotation

In the context of genomics, **annotation** is the process of marking the genes and other biological features in a DNA sequence. The first genome annotation software system was designed in 1995 by Dr. Owen White, who was part of the team at The Institute for Genomic Research that sequenced and analyzed the first genome of a free-living organism to be decoded, the bacterium *Haemophilus influenzae*. Dr. White built a software system to find the genes (places in the DNA sequence that encode a protein), the transfer RNA, and other features, and to make initial assignments of function to those genes. Most current genome annotation systems work similarly, but the programs available for analysis of genomic DNA are constantly changing and improving.

Computational evolutionary biology

Evolutionary biology is the study of the origin and descent of species, as well as their change over time. Informatics has assisted evolutionary biologists in several key ways; it has enabled researchers to:

- trace the evolution of a large number of organisms by measuring changes in their DNA, rather than through physical taxonomy or physiological observations alone,
- more recently, compare entire genomes, which permits the study of more complex evolutionary events, such as gene duplication, horizontal gene transfer, and the prediction of factors important in bacterial speciation,
- build complex computational models of populations to predict the outcome of the system over time
- track and share information on an increasingly large number of species and organisms

Future work endeavours to reconstruct the now more complex tree of life.

The area of research within computer science that uses genetic algorithms is sometimes confused with computational evolutionary biology, but the two areas are unrelated.

Analysis of gene expression

The expression of many genes can be determined by measuring mRNA levels with multiple techniques including microarrays, expressed cDNA sequence tag (EST) sequencing, serial analysis of gene expression (SAGE) tag sequencing, massively parallel signature sequencing (MPSS), or various applications of multiplexed in-situ hybridization. All of these techniques are extremely noise-prone and/or subject to bias in the biological measurement, and a major research area in computational biology involves developing statistical tools to separate signal from noise in high-throughput gene expression studies. Such studies are often used to determine the genes implicated in a disorder: one might compare microarray data from cancerous epithelial cells to data from non-cancerous cells to determine the transcripts that are up-regulated and down-regulated in a particular population of cancer cells.

Analysis of regulation

Regulation is the complex orchestration of events starting with an extracellular signal such as a hormone and leading to an increase or decrease in the activity of one or more proteins. Bioinformatics techniques have been applied to explore various steps in this process. For example, promoter analysis involves the identification and study of sequence motifs in the DNA surrounding the coding region of a gene. These motifs influence the extent to which that region is transcribed into mRNA. Expression data can be used to infer gene regulation: one might compare microarray data from a wide variety of states of an organism to form hypotheses about the genes involved in each state. In a single-cell organism, one might compare stages of the cell cycle, along with various stress conditions (heat shock, starvation, etc.). One can then apply clustering algorithms to that expression data to determine which genes are co-expressed. For example, the upstream regions (promoters) of co-expressed genes can be searched for over-represented regulatory elements.

Analysis of protein expression

Protein microarrays and high throughput (HT) mass spectrometry (MS) can provide a snapshot of the proteins present in a biological sample. Bioinformatics is very much involved in making sense of protein microarray and HT MS data; the former approach faces similar problems as with microarrays targeted at mRNA, the latter involves the problem of matching large amounts of mass data against predicted masses from protein sequence databases, and the complicated statistical analysis of samples where multiple, but incomplete peptides from each protein are detected.

Analysis of mutations in cancer

In cancer, the genomes of affected cells are rearranged in complex or even unpredictable ways. Massive sequencing efforts are used to identify previously unknown point mutations in a variety of genes in cancer. Bioinformaticians continue to produce specialized automated systems to manage the sheer volume of sequence data produced, and they create new algorithms and software to compare the sequencing results to the growing collection of human genome sequences and germline polymorphisms. New physical detection technology are employed, such as oligonucleotide microarrays to identify chromosomal gains and losses (called comparative genomic hybridization), and single-nucleotide polymorphism arrays to detect known *point mutations*. These detection methods simultaneously measure several hundred thousand sites throughout the genome, and when used in high-throughput to measure thousands of samples, generate terabytes of data per experiment. Again the massive amounts and new types of data generate new opportunities for bioinformaticians. The data is often found to contain considerable variability, or noise, and thus Hidden Markov model and change-point analysis methods are being developed to infer real copy number changes.

Another type of data that requires novel informatics development is the analysis of lesions found to be recurrent among many tumors .

Prediction of protein structure

Protein structure prediction is another important application of bioinformatics. The amino acid sequence of a protein, the so-called primary structure, can be easily determined from the sequence on the gene that codes for it. In the vast majority of cases, this primary structure uniquely determines a structure in its native environment. (Of course, there are exceptions, such as the bovine spongiform encephalopathy - aka Mad Cow Disease - prion.) Knowledge of this structure is vital in understanding the function of the protein. For lack of better terms, structural information is usually classified as one of *secondary*, *tertiary* and *quaternary* structure. A viable general solution to such predictions remains an open problem. As of now, most efforts have been directed towards heuristics that work most of the time.

One of the key ideas in bioinformatics is the notion of homology. In the genomic branch of bioinformatics, homology is used to predict the function of a gene: if the sequence of gene *A*, whose function is known, is homologous to the sequence of gene *B,* whose function is unknown, one could infer that B may share A's function. In the structural branch of bioinformatics, homology is used to determine which parts of a protein are important in structure formation and interaction with other proteins. In a technique called homology modeling, this information is used to predict the structure of a protein once the structure of a homologous protein is known. This currently remains the only way to predict protein structures reliably.

One example of this is the similar protein homology between hemoglobin in humans and the hemoglobin in legumes (leghemoglobin). Both serve the same purpose of transporting oxygen in the organism. Though both of these proteins have completely different amino acid sequences, their protein structures are virtually identical, which reflects their near identical purposes.

Other techniques for predicting protein structure include protein threading and *de novo* (from scratch) physics-based modeling.

See also: structural motif and structural domain.

Comparative genomics

The core of comparative genome analysis is the establishment of the correspondence between genes (orthology analysis) or other genomic features in different organisms. It is these intergenomic maps that make it possible to trace the evolutionary processes responsible for the divergence of two genomes. A multitude of evolutionary events acting at various organizational levels shape genome evolution. At the lowest level, point mutations affect individual nucleotides. At a higher level, large chromosomal segments undergo duplication, lateral transfer, inversion, transposition, deletion and insertion. Ultimately, whole genomes are involved in processes of hybridization, polyploidization and endosymbiosis, often leading to rapid speciation. The complexity of genome evolution poses many exciting challenges to developers of mathematical models and algorithms, who have recourse to a spectra of algorithmic, statistical and mathematical techniques, ranging from exact, heuristics, fixed parameter and approximation algorithms for problems based on parsimony models to Markov Chain Monte Carlo algorithms for Bayesian analysis of problems based on probabilistic models.

Many of these studies are based on the homology detection and protein families computation.

Modeling biological systems

Systems biology involves the use of computer simulations of cellular subsystems (such as the networks of metabolites and enzymes which comprise metabolism, signal transduction pathways and gene regulatory networks) to both analyze and visualize the complex connections of these cellular processes. Artificial life or virtual evolution attempts to understand evolutionary processes via the computer simulation of simple (artificial) life forms.

High-throughput image analysis

Computational technologies are used to accelerate or fully automate the processing, quantification and analysis of large amounts of high-information-content biomedical imagery. Modern image analysis systems augment an observer's ability to make measurements from a large or complex set of images, by improving accuracy, objectivity, or speed. A fully developed analysis system may completely replace the observer. Although these systems are not unique to biomedical imagery, biomedical imaging is becoming more important for both diagnostics and research. Some examples are:

- high-throughput and high-fidelity quantification and sub-cellular localization (high-content screening, cytohistopathology)
- morphometrics
- clinical image analysis and visualization
- determining the real-time air-flow patterns in breathing lungs of living animals
- quantifying occlusion size in real-time imagery from the development of and recovery during arterial injury
- making behavioral observations from extended video recordings of laboratory animals
- infrared measurements for metabolic activity determination
- inferring clone overlaps in DNA mapping, e.g. the Sulston score

Protein-protein docking

In the last two decades, tens of thousands of protein three-dimensional structures have been determined by X-ray crystallography and Protein nuclear magnetic resonance spectroscopy (protein NMR). One central question for the biological scientist is whether it is practical to predict possible protein-protein interactions only based on these 3D shapes, without doing protein-protein interaction experiments. A variety of methods have been developed to tackle the Protein-protein docking problem, though it seems that there is still much work to be done in this field.

Software and tools

Software tools for bioinformatics range from simple command-line tools, to more complex graphical programs and standalone web-services available from various bioinformatics companies or public institutions.

Web services in bioinformatics

SOAP and REST-based interfaces have been developed for a wide variety of bioinformatics applications allowing an application running on one computer in one part of the world to use algorithms, data and computing resources on servers in other parts of the world. The main advantages derive from the fact that end users do not have to deal with software and database maintenance overheads.

Basic bioinformatics services are classified by the EBI into three categories: SSS (Sequence Search Services), MSA (Multiple Sequence Alignment) and BSA (Biological Sequence Analysis). The availability of these service-oriented bioinformatics resources demonstrate the applicability of web based bioinformatics solutions, and range from a collection of standalone tools with a common data format under a single, standalone or web-based interface, to integrative, distributed and extensible bioinformatics workflow management systems.

See also

Related topics

- Biocybernetics
- Bioinformatics companies
- Biologically inspired computing
- Biomedical informatics
- Computational biology
- Computational biomodeling
- Computational genomics
- DNA sequencing theory
- Dot plot (bioinformatics)
- Dry lab
- Functional genomics
- Margaret Oakley Dayhoff
- Metabolic network modelling
- Molecular design software
- Molecular modeling on GPU
- Morphometrics
- Natural computation
- Pharmaceutical company
- Protein-protein interaction prediction
- Shredding (disassembling genomic data)
- List of nucleic acid simulation software
- List of numerical analysis software
- List of protein structure prediction software
- List of scientific journals in bioinformatics

Related fields

- Applied mathematics
- Artificial intelligence
- Biodiversity informatics
- Biology
- Cheminformatics
- Clinomics
- Comparative genomics
- Computational biology
- Computational epigenetics
- Computational science
- Computer science
- Cybernetics
- Ecoinformatics
- Functional genomics
- Genomics
- Informatics (academic field)
- Information theory
- Mathematical biology
- Molecular modelling
- Neuroinformatics
- Proteomics
- Pervasive adaptation
- Scientific computing
- Statistics
- Structural biology
- Systems biology
- Theoretical biology
- Veterinary informatics

References

- Achuthsankar S Nair Computational Biology & Bioinformatics - A gentle Overview (http://print.achuth. googlepages.com/BINFTutorialV5.0CSI07.pdf), Communications of Computer Society of India, January 2007
- Aluru, Srinivas, ed. *Handbook of Computational Molecular Biology*. Chapman & Hall/Crc, 2006. ISBN 1584884061 (Chapman & Hall/Crc Computer and Information Science Series)
- Baldi, P and Brunak, S, *Bioinformatics: The Machine Learning Approach*, 2nd edition. MIT Press, 2001. ISBN 0-262-02506-X
- Barnes, M.R. and Gray, I.C., eds., *Bioinformatics for Geneticists*, first edition. Wiley, 2003. ISBN 0-470-84394-2
- Baxevanis, A.D. and Ouellette, B.F.F., eds., *Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins*, third edition. Wiley, 2005. ISBN 0-471-47878-4
- Baxevanis, A.D., Petsko, G.A., Stein, L.D., and Stormo, G.D., eds., *Current Protocols in Bioinformatics*. Wiley, 2007. ISBN 0-471-25093-7
- Claverie, J.M. and C. Notredame, *Bioinformatics for Dummies*. Wiley, 2003. ISBN 0-7645-1696-5
- Cristianini, N. and Hahn, M. *Introduction to Computational Genomics* (http://www.computational-genomics. net/), Cambridge University Press, 2006. (ISBN 9780521671910 | ISBN 0521671914)

- Durbin, R., S. Eddy, A. Krogh and G. Mitchison, *Biological sequence analysis*. Cambridge University Press, 1998. ISBN 0-521-62971-3
- Gilbert, D. *Bioinformatics software resources* (http://bib.oxfordjournals.org/cgi/content/abstract/5/3/300). Briefings in Bioinformatics, Briefings in Bioinformatics, 2004 5(3):300-304.
- Keedwell, E., *Intelligent Bioinformatics: The Application of Artificial Intelligence Techniques to Bioinformatics Problems*. Wiley, 2005. ISBN 0-470-02175-6
- Kohane, et al. *Microarrays for an Integrative Genomics.* The MIT Press, 2002. ISBN 0-262-11271-X
- Lund, O. et al. *Immunological Bioinformatics.* The MIT Press, 2005. ISBN 0-262-12280-4
- Michael S. Waterman, *Introduction to Computational Biology: Sequences, Maps and Genomes*. CRC Press, 1995. ISBN 0-412-99391-0
- Mount, David W. *Bioinformatics: Sequence and Genome Analysis* Spring Harbor Press, May 2002. ISBN 0-87969-608-7
- Pachter, Lior and Sturmfels, Bernd. "Algebraic Statistics for Computational Biology" Cambridge University Press, 2005. ISBN 0-521-85700-7
- Pevzner, Pavel A. *Computational Molecular Biology: An Algorithmic Approach* The MIT Press, 2000. ISBN 0-262-16197-4
- Soinov, L. Bioinformatics and Pattern Recognition Come Together (http://jprr.org/index.php/jprr/article/view/8/5) Journal of Pattern Recognition Research (JPRR (http://www.jprr.org)), Vol 1 (1) 2006 p.37-41
- Tisdall, James. "Beginning Perl for Bioinformatics" O'Reilly, 2001. ISBN 0-596-00080-4
- Dedicated issue of *Philosophical Transactions B* on Bioinformatics freely available (http://publishing.royalsociety.org/bioinformatics)
- Catalyzing Inquiry at the Interface of Computing and Biology (2005) CSTB report (http://www.nap.edu/catalog/11480.html)
- Calculating the Secrets of Life: Contributions of the Mathematical Sciences and computing to Molecular Biology (1995) (http://www.nap.edu/catalog/2121.html)
- Foundations of Computational and Systems Biology MIT Course (http://ocw.mit.edu/OcwWeb/Biology/7-91JSpring2004/LectureNotes/index.htm)
- Computational Biology: Genomes, Networks, Evolution Free MIT Course (http://ocw.mit.edu/OcwWeb/Electrical-Engineering-and-Computer-Science/6-895Fall-2005/CourseHome/index.htm)
- Algorithms for Computational Biology Free MIT Course (http://ocw.mit.edu/OcwWeb/Electrical-Engineering-and-Computer-Science/6-096Spring-2005/CourseHome/index.htm)
- Zhang, Z., Cheung, K.H. and Townsend, J.P. Bringing Web 2.0 to bioinformatics, Briefing in Bioinformatics. In press (http://www.ncbi.nlm.nih.gov/pubmed/18842678)

External links

- Major Organizations
  - Bioinformatics Organization (Bioinformatics.Org): The Open-Access Institute (http://bioinformatics.org/)
  - EMBnet (http://www.embnet.org/)
  - European Bioinformatics Institute (http://www.ebi.ac.uk/)
  - European Molecular Biology Laboratory (http://www.embl.org/)
  - The International Society for Computational Biology (http://www.iscb.org/)
  - National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/)
  - Open Bioinformatics Foundation: umbrella non-profit organization supporting certain open-source projects in bioinformatics (http://www.open-bio.org/)
  - Swiss Institute of Bioinformatics
  - Wellcome Trust Sanger Institute

- Major Journals

  - Algorithms in Molecular Biology (http://www.almob.org/)
  - Bioinformatics (http://bioinformatics.oupjournals.org/)
  - BMC Bioinformatics (http://www.biomedcentral.com/bmcbioinformatics)
  - Briefings in Bioinformatics (http://bib.oxfordjournals.org/)
  - Journal of Advanced Research in Bioinformatics (http://www.i-asr.org/jarb.html)
  - Evolutionary Bioinformatics (http://www.la-press.com/evolbio.htm)
  - Genome Research (http://www.genome.org)
  - The International Journal of Biostatistics (http://www.bepress.com/ijb/)
  - Journal of Computational Biology (http://www.liebertpub.com/publication.aspx?pub_id=31)
  - Cancer Informatics (http://la-press.com/journal.php?pa=description&journal_id=10)
  - Molecular Systems Biology (http://www.nature.com/msb/index.html)
  - PLoS Computational Biology (http://compbiol.plosjournals.org)
  - Statistical Applications in Genetic and Molecular Biology (http://www.bepress.com/sagmb/)
  - Transactions on Computational Biology and Bioinformatics - IEEE/ACM (http://www.computer.org/tcbb/)
  - International Journal of Bioinformatics Research and Applications (http://www.inderscience.com/browse/index.php?journalcode=ijbra)
  - International Journal of Computational Biology and Drug Design (IJCBDD)
  - International Journal of Functional Informatics and Personalized Medicine (IJFIPM)

- Other sites

  - The exhaustive bioinformatics information resource directory including servers, tools, database links and bioinformatics companies (http://bionet.awardspace.info/)
  - The Collection of Biostatistics Research Archive (http://www.biostatsresearch.com/repository/)
  - Human Genome Project and Bioinformatics (http://www.ornl.gov/TechResources/Human_Genome/research/informatics.html)
  - List of Bioinformatics Research Groups (http://www.bioinformatics.fr/laboratories.php) at Bioinformatics.fr
  - List of Bioinformatics Research Groups (http://www.dmoz.org/Science/Biology/Bioinformatics/Research_Groups//) at the Open Directory Project

- Tutorials / Resources / Primers

  - Bioinformatics - A Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/bioinformatics.html) — by NCBI
  - A bioinformatics directory (http://bioinformatics.co.nr/)
  - Canadian Bioinformatics Workshop and Links Directory (http://bioinformatics.ca/)

See also

- International Society of Intelligent Biological Medicine (ISIBM)

X-ray diffraction

X-ray scattering techniques are a family of non-destructive analytical techniques which reveal information about the crystallographic structure, chemical composition, and physical properties of materials and thin films. These techniques are based on observing the scattered intensity of an X-ray beam hitting a sample as a function of incident and scattered angle, polarization, and wavelength or energy.

X-ray diffraction techniques

X-ray diffraction finds the geometry or shape of a molecule using X-rays. X-ray diffraction techniques are based on the elastic scattering of X-rays from structures that have long range order. The most comprehensive description of scattering from crystals is given by the dynamical theory of diffraction.[1]

This is an X-ray diffraction pattern formed when X-rays are focused on a crystalline material, in this case a protein. Each dot, called a reflection, forms from the coherent interference of scattered X-rays passing through the crystal.

- Single-crystal X-ray diffraction is a technique used to solve the complete structure of crystalline materials, ranging from simple inorganic solids to complex macromolecules, such as proteins.

- Powder diffraction (XRD) is a technique used to characterise the crystallographic structure, crystallite size (grain size), and preferred orientation in polycrystalline or powdered solid samples. Powder diffraction is commonly used to identify unknown substances, by comparing diffraction data against a database maintained by the International Centre for Diffraction Data. It may also be used to characterize heterogeneous solid mixtures to determine relative abundance of crystalline compounds and, when coupled with lattice refinement techniques, such as Rietveld refinement, can provide structural information on unknown materials. Powder diffraction is also a common method for determining strains in crystalline materials. An effect of the finite crystallite sizes is seen as a broadening of the peaks in an X-ray diffraction as is explained by the Scherrer Equation.

- Thin film diffraction and grazing incidence X-ray diffraction may be used to characterize the crystallographic structure and preferred orientation of substrate-anchored thin films.

- High-resolution X-ray diffraction is used to characterize thickness, crystallographic structure, and strain in thin epitaxial films. It employs parallel-beam optics.

- X-ray pole figure analysis enables one to analyze and determine the distribution of crystalline orientations within a crystalline thin-film sample.

- X-ray rocking curve analysis is used to quantify grain size and mosaic spread in crystalline materials.
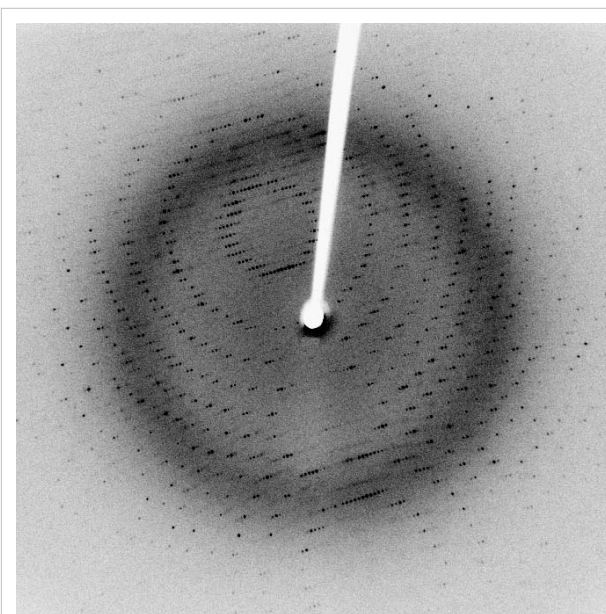
Scattering techniques

Elastic scattering

Materials that do not have long range order may also be studied by scattering methods that rely on elastic scattering of monochromatic X-rays.

- Small angle X-ray scattering (SAXS) probes structure in the nanometer to micrometer range by measuring scattering intensity at scattering angles 2θ close to 0°.[2]
- X-ray reflectivity is an analytical technique for determining thickness, roughness, and density of single layer and multilayer thin films.
- Wide angle X-ray scattering (WAXS), a technique concentrating on scattering angles 2θ larger than 5°.

Inelastic scattering

When the energy and angle of the inelastically scattered X-rays are monitored scattering techniques can be used to probe the electronic band structure of materials.

- Compton scattering
- Resonant inelastic X-ray scattering (RIXS)
- X-ray Raman scattering
- X-ray diffraction pattern

See also

- Structure determination
- Materials Science
- Metallurgy
- Mineralogy
- X-ray crystallography
- X-ray generator

External links

- International Union of Crystallography [3]
  - IUCr Crystallography Online [4]
- The International Centre for Diffraction Data (ICDD) [5]
- Archives of XRD@JISCMAIL.AC.UK [6]
- The British Crystallographic Association [7]
- Introduction to X-ray Diffraction [8] at University of California, Santa Barbara

References

[1] Azároff, L. V.; R. Kaplow, N. Kato, R. J. Weiss, A. J. C. Wilson, R. A. Young (1974). *X-ray diffraction*. McGraw-Hill.

[2] Glatter, O.; O. Kratky (1982). *Small Angle X-ray Scattering* (http://physchem.kfunigraz.ac.at/sm/Software.htm). Academic Press. .

[3] http://www.iucr.ac.uk/

[4] http://www.iucr.org/cww-top/crystal.index.html

[5] http://www.icdd.com/

[6] http://www.jiscmail.ac.uk/lists/xrd.html

[7] http://crystallography.org.uk/

[8] http://www.mrl.ucsb.edu/mrl/centralfacilities/xray/xray-basics/index.html

Nuclear magnetic resonance

Nuclear magnetic resonance (**NMR**) is a property that magnetic nuclei have in a magnetic field and applied electromagnetic (EM) pulse or pulses, which cause the nuclei to absorb energy from the EM pulse and radiate this energy back out. The energy radiated back out is at a specific resonance frequency which depends on the strength of the magnetic field and other factors. This allows the observation of specific quantum mechanical magnetic properties of an atomic nucleus. Many scientific techniques exploit NMR phenomena to study molecular physics, crystals and non-crystalline materials through NMR spectroscopy. NMR is also routinely used in advanced medical imaging techniques, such as in magnetic resonance imaging (MRI).

All stable nuclides that contain an odd number of protons and/or of neutrons (see Isotope) have an intrinsic magnetic moment and angular momentum, in other words a nonzero spin, while all nuclides with even numbers of both have spin 0. The most commonly studied nuclei are ^{1}H (the most NMR-sensitive isotope after the radioactive ^{3}H) and ^{13}C, although nuclei from isotopes of many other elements (e.g. ^{2}H, ^{10}B, ^{11}B, ^{14}N, ^{15}N, ^{17}O, ^{19}F, ^{23}Na, ^{29}Si, ^{31}P, ^{35}Cl, ^{113}Cd, ^{195}Pt) are studied by high-field NMR spectroscopy as well.

World's First 1 GHz NMR Spectrometer (1000 MHz, 23.5 T) was installed at the new 'Centre de RMN à Très Hauts Champs' in Lyon, France in August 2009

A key feature of NMR is that the resonance frequency of a particular substance is directly proportional to the strength of the applied magnetic field. It is this feature that is exploited in imaging techniques; if a sample is placed in a non-uniform magnetic field then the resonance frequencies of the sample's nuclei depend on where in the field they are located. Since the resolution of the imaging techniques depends on how big the gradient of the field is, many efforts are made to develop more powerful magnets, often using superconductors. The effectiveness of NMR can also be improved using hyperpolarization, and/or using two-dimensional, three-dimensional and higher dimension multi-frequency techniques.

Pacific Northwest National Laboratory's high magnetic field (800 MHz, 18.8 T) NMR spectrometer.

The principle of NMR usually involves two sequential steps:

- The alignment (polarization) of the magnetic nuclear spins in an applied, constant magnetic field $\mathbf{H}_0$.
- The perturbation of this alignment of the nuclear spins by employing an electro-magnetic, usually radio frequency (RF) pulse. The required perturbing frequency is dependent upon the static magnetic field ($\mathbf{H}_0$) and the nuclei of observation.

The two fields are usually chosen to be perpendicular to each other as this maximizes the NMR signal strength. The resulting response by the total magnetization ($\mathbf{M}$) of the nuclear spins is the phenomenon that is exploited in NMR spectroscopy and magnetic resonance imaging. Both use intense applied magnetic fields ($\mathbf{H}_0$) in order to achieve dispersion and very high stability to deliver spectral resolution, the details of which are described by chemical shifts, the Zeeman effect, and Knight shifts (in metals).

NMR phenomena are also utilized in low-field NMR, NMR spectroscopy and MRI in the Earth's magnetic field (referred to as Earth's field NMR), and in several types of magnetometers.

History

Discovery

Nuclear magnetic resonance was first described and measured in molecular beams by Isidor Rabi in 1938.[1] Eight years later, in 1946, Felix Bloch and Edward Mills Purcell refined the technique for use on liquids and solids, for which they shared the Nobel Prize in physics in 1952.[2]

Purcell had worked on the development and radar applications during World War II at Massachusetts Institute of Technology's Radiation Laboratory. His work during that project on the production and detection of RF energy, and on the absorption of such RF energy by matter, preceded his discovery of NMR.

They noticed that magnetic nuclei, like ^{1}H and ^{31}P, could absorb RF energy when placed in a magnetic field of a strength specific to the identity of the nuclei. When this absorption occurs, the nucleus is described as being *in resonance*. Different atomic nuclei within a molecule resonate at different (radio) frequencies for the same magnetic field strength. The observation of such magnetic resonance frequencies of the nuclei present in a molecule allows any trained user to discover essential, chemical and structural information about the molecule.

The development of nuclear magnetic resonance as a technique of analytical chemistry and biochemistry parallels the development of electromagnetic technology and its introduction into civilian use.

Theory of nuclear magnetic resonance

Nuclear spin and magnets

All nucleons, that is neutrons and protons, composing any atomic nucleus, have the intrinsic quantum property of spin. The overall spin of the nucleus is determined by the spin quantum number S. If the number of both the protons and neutrons in a given nuclide are even then $S = 0$, i.e. there is no overall spin; just as electrons pair up in atomic orbitals, so do even numbers of protons or even numbers of neutrons (which are also spin-$\frac{1}{2}$ particles and hence fermions) pair up giving zero overall spin.

However, a proton and neutron will have lower energy when their spins are parallel, **not anti-parallel**, as this parallel spin alignment does not infringe upon the Pauli principle, but instead has to do with the quark fine structure of these two nucleons. Therefore, the spin ground state for the deuteron (the deuterium nucleus, or the ^{2}H isotope of hydrogen)—that has only a proton and a neutron—corresponds to a spin value of **1**, *not of zero*; the single, isolated deuteron is therefore exhibiting an NMR absorption spectrum characteristic of a quadrupolar nucleus of spin **1**, which in the 'rigid' state at very low temperatures is a characteristic ('Pake') *doublet*, (not a singlet as for a single, isolated ^{1}H, or any other isolated fermion or dipolar nucleus of spin 1/2). On the other hand, because of the Pauli principle, the (radioactive) tritium isotope has to have a pair of anti-parallel spin neutrons (of total spin zero for the neutron spin couple), plus a proton of spin 1/2; therefore, the character of the tritium nucleus ('triton') is again magnetic dipolar, *not quadrupolar*—like its non-radioactive deuteron neighbor, and the tritium nucleus total spin value is again 1/2, just like for the simpler, abundant hydrogen isotope, ^{1}H nucleus (the *proton*). The NMR absorption (radio) frequency for tritium is however slightly higher for tritium than that of ^{1}H because the tritium nucleus has a slightly higher gyromagnetic ratio than ^{1}H. In many other cases of *non-radioactive* nuclei, the overall spin is also non-zero. For example, the ^{27}Al nucleus has an overall spin value $S = \frac{5}{2}$.

A non-zero spin is thus always associated with a non-zero magnetic moment (μ) via the relation $\mu = \gamma S$, where γ is the gyromagnetic ratio. It is this magnetic moment that allows the observation of NMR absorption spectra caused by transitions between nuclear spin levels. Most nuclides (with some rare exceptions) that have both even numbers of protons and even numbers of neutrons, also have zero nuclear magnetic moments-and also have zero magnetic dipole and quadrupole moments; therefore, such nuclides do not exhibit any NMR absorption spectra. Thus, ^{18}O is an example of a nuclide that has no NMR absorption, whereas ^{13}C, ^{31}P, ^{35}Cl and ^{37}Cl are nuclides that do exhibit NMR absorption spectra; the last two nuclei are quadrupolar nuclei whereas the preceding two nuclei (^{13}C and ^{31}P) are dipolar ones.

Electron spin resonance (ESR) is a related technique which detects transitions between electron spin levels instead of nuclear ones. The basic principles are similar; however, the instrumentation, data analysis and detailed theory are significantly different. Moreover, there is a much smaller number of molecules and materials with unpaired electron spins that exhibit ESR (or electron paramagnetic resonance (EPR)) absorption than those that have NMR absorption spectra. Significantly also, is the much greater sensitivity of ESR and EPR in comparison with NMR. Furthermore, ferromagnetic materials and thin films may exhibit 'very unusual', highly resolved ferromagnetic resonance (FMR) spectra, or ferromagnetic spin wave resonance (FSWR) excitations in non-crystalline solids such as ferromagnetic metallic glasses, well beyond the common single-transitions of most routine NMR, FMR and EPR studies.[3] [4]

Values of spin angular momentum

The angular momentum associated with nuclear spin is quantized. This means both that the magnitude of angular momentum is quantized (i.e. S can only take on a restricted range of values), and also that the orientation of the associated angular momentum is quantized. The associated quantum number is known as the magnetic quantum number, m, and can take values from $+S$ to $-S$, in integer steps. Hence for any given nucleus, there is a total of $2S + 1$ angular momentum states.

The z-component of the angular momentum vector (**S**) is therefore $S_z = m\hbar$, where $\hbar$ is the reduced Planck constant. The z-component of the magnetic moment is simply:

$$\mu_z = gS_z = gm\hbar$$

Spin behavior in a magnetic field

Consider nuclei which have a spin of one-half, like ^{1}H, ^{13}C or ^{19}F. The nucleus has two possible spin states: $m = \frac{1}{2}$ or $m = -\frac{1}{2}$ (also referred to as spin-up and spin-down, or sometimes α and β spin states, respectively). These states are degenerate, that is they have the same energy. Hence the number of atoms in these two states will be approximately equal at thermal equilibrium.

If a nucleus is placed in a magnetic field, however, the interaction between the nuclear magnetic moment and the external magnetic field mean the two states no longer have the same energy. The energy of a magnetic moment $\boldsymbol{\mu}$ when in a magnetic field $\mathbf{B}_0$ is given by:

$$E = -\mu \cdot \mathbf{B}_0 = -\mu_z B_0 \cos\theta \ .$$

Usually $\mathbf{B}_0$ is chosen to be aligned along the z axis, therefore $\cos\theta = 1$:

$$E = -\mu_z B_0 \ ,$$

or alternatively:

$$E = -gm\hbar B_0 \ .$$

As a result the different nuclear spin states have different energies in a non-zero magnetic field. In hand-waving terms, we can talk about the two spin states of a spin $\frac{1}{2}$ as being *aligned* either with or against the magnetic field. If g is positive (true for most isotopes) then $m = \frac{1}{2}$ is the lower energy state.

The energy difference between the two states is:

$$\Delta E = g\hbar B_0 \ ,$$

and this difference results in a small population bias toward the lower energy state.
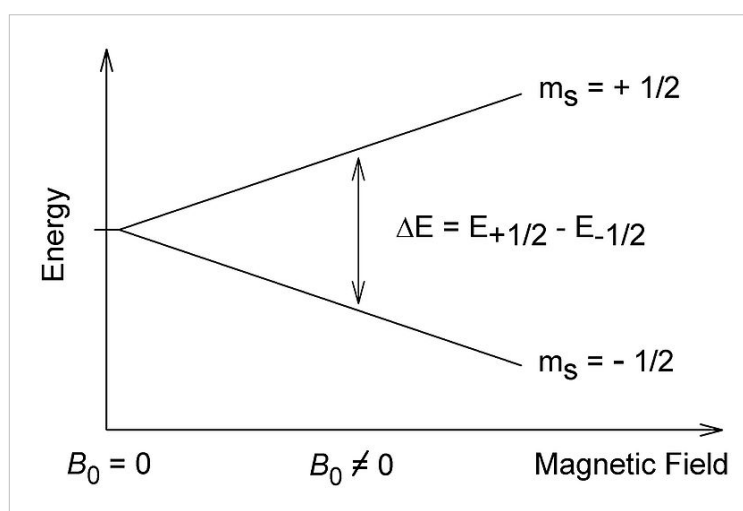
Magnetic resonance by nuclei

Resonant absorption by nuclear spins will occur only when electromagnetic radiation of the correct frequency (e.g., equaling the Larmor precession rate) is being applied to match the energy difference between the nuclear spin levels in a constant magnetic field of the appropriate strength. The energy of an absorbed photon is then $E = h\nu_0$, where ν_0 is the resonance radiofrequency that has to match (that is, it has to be equal to) the Larmor precession frequency ν_L of the nuclear magnetization in the constant magnetic field $\mathbf{B}_0$. Hence, a magnetic resonance absorption will only

occur when $\Delta E = h\nu_0$, which is when $\nu_0 = gB_0/(2\pi)$. Such magnetic resonance frequencies typically correspond to the radio frequency (or RF) range of the electromagnetic spectrum for magnetic fields up to ~20 T. It is this magnetic resonant absorption which is detected in NMR.

Nuclear shielding

It might appear from the above that all nuclei of the same nuclide (and hence the same g) would resonate at the same frequency. This is not the case. The most important perturbation of the NMR frequency for applications of NMR is the 'shielding' effect of the surrounding electrons. In general, this electronic shielding reduces the magnetic field *at the nucleus* (which is what determines the NMR frequency).

As a result the energy gap is reduced, and the frequency required to achieve resonance is also reduced. This shift in the NMR frequency due to the electrons' molecular orbital coupling to the external magnetic field is called chemical shift, and it explains why NMR is able to probe the chemical structure of molecules which depends on the electron density distribution in the corresponding molecular orbitals. If a nucleus in a specific chemical group is shielded to a higher degree by a higher electron density of its surrounding molecular orbital, then its NMR frequency will be shifted "upfield" (that is, a lower chemical shift), whereas if it is less shielded by such surrounding electron density, then its NMR frequency will be shifted "downfield" (that is, a higher chemical shift).

Unless the local symmetry of such molecular orbitals is very high (leading to "isotropic" shift), the shielding effect will depend on the orientation of the molecule with respect to the external field ($\mathbf{B}_0$). In solid-state NMR spectroscopy, magic angle spinning is required to average out this orientation dependence in order to obtain values close to the average chemical shifts. This is unnecessary in conventional NMR investigations of molecules, since rapid molecular tumbling averages out the chemical shift anisotropy (CSA). In this case, the term "average" chemical shift (ACS) is used.

Relaxation

The process called population relaxation refers to nuclei that return to the thermodynamic state in the magnet. This process is also called T_1, "spin-lattice" or "longitudinal magnetic" relaxation, where T_1 refers to the mean time for an individual nucleus to return to its thermal equilibrium state of the spins. Once the nuclear spin population is relaxed, it can be probed again, since it is in the initial, equilibrium (mixed) state.

The precessing nuclei can also fall out of alignment with each other (returning the net magnetization vector to a non-precessing field) and stop producing a signal. This is called T_2 or *transverse relaxation*. Because of the difference in the actual relaxation mechanisms involved (for example, inter-molecular vs. intra-molecular magnetic dipole-dipole interactions), T_1 is always longer than T_2 (that is, slower spin-lattice relaxation, for example because of smaller dipole-dipole interaction effects). In practice, the value of T_2^* which is the actually observed decay time of the observed NMR signal, or free induction decay, (to 1/e of the initial amplitude immediately after the resonant RF pulse)-- also depends on the static magnetic field inhomogeneity, which is quite significant. (There is also a smaller but significant contribution to the observed FID shortening from the RF inhomogeneity of the resonant pulse). In the corresponding FT-NMR spectrum—meaning the Fourier transform of the free induction decay--the T_2^* time is inversely related to the width of the NMR signal in frequency units. Thus, a nucleus with a long T_2 relaxation time gives rise to a very sharp NMR peak in the FT-NMR spectrum for a very homogeneous ("well-shimmed") static magnetic field, whereas nuclei with shorter T_2 values give rise to broad FT-NMR peaks even when the magnet is shimmed well. Both T_1 and T_2 depend on the rate of molecular motions as well as the gyromagnetic ratios of both the resonating and their strongly interacting, next-neighbor nuclei that are not at resonance.

NMR spectroscopy

NMR spectroscopy is one of the principal techniques used to obtain physical, chemical, electronic and structural information about molecules due to either the chemical shift, Zeeman effect, or the Knight shift effect, or a combination of both, on the resonant frequencies of the nuclei present in the sample. It is a powerful technique that can provide detailed information on the topology, dynamics and three-dimensional structure of molecules in solution and the solid state. Thus, structural and dynamic information is obtainable (with or without "magic angle" spinning (MAS)) from NMR studies of quadrupolar nuclei (that is, those nuclei with spin $S > \frac{1}{2}$) even in the presence of magnetic dipole-dipole interaction broadening (or simply, dipolar broadening) which is always much smaller than the quadrupolar interaction strength because it is a magnetic vs. an electric interaction effect.

Additional structural and chemical information may be obtained by performing double-quantum NMR experiments for quadrupolar nuclei such as ^{2}H. Also, nuclear magnetic resonance is one of the techniques that has been used to design quantum automata, and also build elementary quantum computers.[5] [6]

900MHz, 21.2 T NMR Magnet at HWB-NMR, Birmingham, UK

Continuous wave (CW) spectroscopy

In its first few decades, nuclear magnetic resonance spectrometers used a technique known as continuous-wave spectroscopy (CW spectroscopy). Although NMR spectra could be, and have been, obtained using a fixed magnetic field and sweeping the frequency of the electromagnetic radiation, this more typically involved using a fixed frequency source and varying the current (and hence magnetic field) in an electromagnet to observe the resonant absorption signals. This is the origin of the counterintuitive, but still common, "high" and "low" field terminology for low frequency and high frequency regions respectively of the NMR spectrum.

CW spectroscopy is inefficient in comparison to Fourier techniques (see below) as it probes the NMR response at individual frequencies in succession. As the NMR signal is intrinsically weak, the observed spectra suffer from a poor signal-to-noise ratio. This can be mitigated by signal averaging i.e. adding the spectra from repeated measurements. While the NMR signal is constant between scans and so adds linearly, the random noise adds more slowly—as the square-root of the number of spectra (see Random walk). Hence the overall ratio of the signal to the noise increases as the square-root of the number of spectra measured.

Fourier transform spectroscopy

Most applications of NMR involve full NMR spectra, that is, the intensity of the NMR signal as a function of frequency. Early attempts to acquire the NMR spectrum more efficiently than simple CW methods involved irradiating simultaneously with more than one frequency. A revolution in NMR occurred when short pulses of radio-frequency were used (centered at the middle of the NMR spectrum). In simple terms, a short square pulse of a given "carrier" frequency "contains" a range of frequencies centered about the carrier frequency, with the range of excitation (bandwidth) being inversely proportional to the pulse duration (the Fourier transform (FT) of an approximate square wave contains contributions from all the frequencies in the neighborhood of the principal frequency). The restricted range of the NMR frequencies made it relatively easy to use short (millisecond to microsecond) radiofrequency (RF) pulses to excite the entire NMR spectrum.

Applying such a pulse to a set of nuclear spins simultaneously excites all the single-quantum NMR transitions. In terms of the net magnetization vector, this corresponds to tilting the magnetization vector away from its equilibrium position (aligned along the external magnetic field). The out-of-equilibrium magnetization vector precesses about the external magnetic field vector at the NMR frequency of the spins. This oscillating magnetization vector induces a current in a nearby pickup coil, creating an electrical signal oscillating at the NMR frequency. This signal is known as the free induction decay (FID) and contains the vector-sum of the NMR responses from all the excited spins. In order to obtain the frequency-domain NMR spectrum (NMR absorption intensity vs. NMR frequency) this time-domain signal (intensity vs. time) must be FTed. Fortunately the development of FT NMR coincided with the development of digital computers and Fast Fourier Transform algorithms. FT methods can be applied to many types of spectroscopy; see the general article on Fourier transform spectroscopy.

Richard R. Ernst was one of the pioneers of pulse (FT) NMR and won a Nobel Prize in chemistry in 1991 for his work on FT NMR and his development of multi-dimensional NMR (see below).

Multi-dimensional NMR Spectroscopy

The use of pulses of different shapes, frequencies and durations in specifically-designed patterns or *pulse sequences* allows the spectroscopist to extract many different types of information about the molecule. Multi-dimensional nuclear magnetic resonance spectroscopy is a kind of FT NMR in which there are at least two pulses and, as the experiment is repeated, the pulse sequence is varied. In *multidimensional nuclear magnetic resonance* there will be a sequence of pulses and, at least, one variable time period. In three dimensions, two time sequences will be varied. In four dimensions, three will be varied.

There are many such experiments. In one, these time intervals allow (amongst other things) magnetization transfer between nuclei and, therefore, the detection of the kinds of nuclear-nuclear interactions that allowed for the magnetization transfer. Interactions that can be detected are usually classified into two kinds. There are *through-bond* interactions and *through-space* interactions, the latter usually being a consequence of the nuclear Overhauser effect. Experiments of the nuclear Overhauser variety may be employed to establish distances between atoms, as for example by 2D-FT NMR of molecules in solution.

Although the fundamental concept of 2D-FT NMR was proposed by Professor Jean Jeener from the Free University of Brussels at an International Conference, this idea was largely developed by Richard Ernst who won the 1991 Nobel prize in Chemistry for his work in FT NMR, including multi-dimensional FT NMR, and especially 2D-FT NMR of small molecules.[7] Multi-dimensional FT NMR experiments were then further developed into powerful methodologies for studying biomolecules in solution, in particular for the determination of the structure of biopolymers such as proteins or even small nucleic acids.[8]

Kurt Wüthrich shared (with John B. Fenn) in 2002 the Nobel Prize in Chemistry for his work in protein FT NMR in solution.

Solid-state NMR spectroscopy

This technique complements biopolymer X-ray crystallography in that it is frequently applicable to biomolecules in a liquid or liquid crystal phase, whereas crystallography, as the name implies, is performed on molecules in a solid phase. Though nuclear magnetic resonance is used to study solids, extensive atomic-level biomolecular structural detail is especially challenging to obtain in the solid state. There is little signal averaging by thermal motion in the solid state, where most molecules can only undergo restricted vibrations and rotations at room temperature, each in a slightly different electronic environment, therefore exhibiting a different NMR absorption peak. Such a variation in the electronic environment of the resonating nuclei results in a blurring of the observed spectra—which is often only a broad Gaussian band for non-quadrupolar spins in a solid- thus making the interpretation of such "dipolar" and "chemical shift anisotropy" (CSA) broadened spectra either very difficult or impossible.

Professor Raymond Andrew at Nottingham University in UK pioneered the development of high-resolution solid-state nuclear magnetic resonance. He was the first to report the introduction of the MAS (magic angle sample spinning; MASS) technique that allowed him to achieve spectral resolution in solids sufficient to distinguish between chemical groups with either different chemical shifts or distinct Knight shifts. In MASS, the sample is spun at several kilohertz around an axis that makes the so-called magic angle θ_m (which is ~54.74°, where $\cos^2\theta_m = 1/3$) with respect to the direction of the static magnetic field $\mathbf{B}_0$; as a result of such magic angle sample spinning, the chemical shift anisotropy bands are averaged to their corresponding average (isotropic) chemical shift values. The above expression involving $\cos^2\theta_m$ has its origin in a calculation that predicts the magnetic dipolar interaction effects to cancel out for the specific value of θ_m called the magic angle. One notes that correct alignment of the sample rotation axis as close as possible to θ_m is essential for cancelling out the dipolar interactions whose strength for angles sufficiently far from θ_m is usually greater than ~10 kHz for C-H bonds in solids, for example, and it is thus greater than their CSA values.

There are different angles for the sample spinning relative to the applied field for the averaging of quadrupole interactions and paramagnetic interactions, correspondingly ~30.6° and ~70.1°

A concept developed by Sven Hartmann and Erwin Hahn was utilized in transferring magnetization from protons to less sensitive nuclei (popularly known as cross-polarization) by M.G. Gibby, Alex Pines and John S. Waugh. Then, Jake Schaefer and Ed Stejskal demonstrated also the powerful use of cross-polarization under MASS conditions which is now routinely employed to detect low-abundance and low-sensitivity nuclei.

Sensitivity

Because the intensity of nuclear magnetic resonance signals and, hence, the sensitivity of the technique depends on the strength of the magnetic field the technique has also advanced over the decades with the development of more powerful magnets. Advances made in audio-visual technology have also improved the signal-generation and processing capabilities of newer machines.

As noted above, the sensitivity of nuclear magnetic resonance signals is also dependent on the presence of a magnetically-susceptible nuclide and, therefore, either on the natural abundance of such nuclides or on the ability of the experimentalist to artificially enrich the molecules, under study, with such nuclides. The most abundant naturally-occurring isotopes of hydrogen and phosphorus (for example) are both magnetically susceptible and readily useful for nuclear magnetic resonance spectroscopy. In contrast, carbon and nitrogen have useful isotopes but which occur only in very low natural abundance.

Other limitations on sensitivity arise from the quantum-mechanical nature of the phenomenon. For quantum states separated by energy equivalent to radio frequencies, thermal energy from the environment causes the populations of the states to be close to equal. Since incoming radiation is equally likely to cause stimulated emission (a transition from the upper to the lower state) as absorption, the NMR effect depends on an excess of nuclei in the lower states. Several factors can reduce sensitivity, including

- Increasing temperature, which evens out the population of states. Conversely, low temperature NMR can sometimes yield better results than room-temperature NMR, providing the sample remains liquid.
- Saturation of the sample with energy applied at the resonant radiofrequency. This manifests in both CW and pulsed NMR; in the first, CW, case this happens by using too much continuous power that keeps the upper spin levels completely populated; in the second case, saturation occurs by pulsing too frequently—without allowing time for the nuclei to return to thermal equilibrium through spin-lattice relaxation. For nuclei such as ^{29}Si this is a serious practical problem as the relaxation time is measured in seconds; for protons in "pure" ice, or ^{19}F in high-purity (undoped) LiF crystals the spin-lattice relaxation time can be on the order of an hour or longer. The use of shorter RF pulses that tip the magnetization by less than 90° can partially solve the problem by allowing spectral acquisition without the complete loss of NMR signal.
- Non-magnetic effects, such as electric-quadrupole coupling of spin-1 and spin-$\frac{3}{2}$ nuclei with their local environment, which broaden and weaken absorption peaks. ^{14}N, an abundant spin-1 nucleus, is difficult to study for this reason. High resolution NMR instead probes molecules using the rarer ^{15}N isotope, which has spin-$\frac{1}{2}$.

Isotopes

Many chemical elements can be used for NMR analysis.[9]

Commonly used nuclei:

- ^{1}H, the most commonly used spin ½ nucleus in NMR investigation, has been studied using many forms of NMR. Hydrogen is highly abundant, especially in biological systems. It is the nucleus most sensitive to NMR signal (apart from ^{3}H which is not commonly used due to its instability and radioactivity). Proton NMR produces narrow chemical shift with sharp signals. The ^{1}H signal has been the sole diagnostic nucleus used for clinical magnetic resonance imaging.
- ^{2}H, a spin 1 nucleus commonly utilized as signal-free medium in the form of deuterated solvents during proton NMR, to avoid signal interference from hydrogen-containing solvents in measurement of ^{1}H solutes. Also used in determining the behavior of lipids in lipid membranes and other solids or liquid crystals as it is a relatively non-perturbing label which can selectively replace ^{1}H. Alternatively, ^{2}H can be detected in media specially labeled with ^{2}H.
- ^{3}He, is very sensitive to NMR. There is a very low percentage in natural helium, and subsequently has to be purified from ^{4}He. It is used mainly in studies of endohedral fullerenes, where its chemical inertness is beneficial to ascertaining the structure of the entrapping fullerene.
- ^{10}B, lower sensitivity than ^{11}B. Quartz tubes must be used as borosilicate glass interferes with measurement.
- ^{11}B, more sensitive than ^{10}B, yields sharper signals. Quartz tubes must be used as borosilicate glass interferes with measurement.
- ^{13}C spin-1/2, is widely used, despite its relative paucity in naturally-occurring carbon (approximately 1%). It is stable to nuclear decay. Since there is a low percentage in natural carbon, spectrum acquisition on samples which have not been experimentally enriched in ^{13}C takes a long time. Frequently used for labeling of compounds in synthetic and metabolic studies. Has low sensitivity and wide chemical shift, yields sharp signals. Low percentage makes it useful by preventing spin-spin couplings and makes the spectrum appear less crowded. Slow relaxation means that spectra are not integrable unless long acquisition times are used.
- ^{14}N, spin-1, medium sensitivity nucleus with wide chemical shift. Its large quadrupole moment interferes in acquisition of high resolution spectra, limiting usefulness to smaller molecules and functional groups with a high degree of symmetry such as the headgroups of lipids.
- ^{15}N, spin-1/2, relatively commonly used. Can be used for labeling compounds. Nucleus very insensitive but yields sharp signals. Low percentage in natural nitrogen together with low sensitivity requires high concentrations or expensive isotope enrichment.
- ^{17}O, spin-5/2, low sensitivity and very low natural abundance (0.037%), wide chemical shifts range (up to 2000 ppm). Quadrupole moment causing a line broadening. Used in metabolic and biochemical studies in studies of

chemical equilibria.

- ^{19}F, spin-1/2, relatively commonly measured. Sensitive, yields sharp signals, has wide chemical shift.
- ^{31}P, spin-1/2, 100% of natural phosphorus. Medium sensitivity, wide chemical shifts range, yields sharp lines. Used in biochemical studies.
- ^{35}Cl and ^{37}Cl, broad signal. ^{35}Cl significantly more sensitive, preferred over ^{37}Cl despite its slightly broader signal. Organic chlorides yield very broad signals, its use is limited to inorganic and ionic chlorides and very small organic molecules.
- ^{43}Ca, used in biochemistry to study calcium binding to DNA, proteins, etc. Moderately sensitive, very low natural abundance.
- ^{195}Pt, used in studies of catalysts and complexes.

Other nuclei (usually used in the studies of their complexes and chemical binding, or to detect presence of the element):

- ^{6}Li, ^{7}Li
- ^{9}Be
- ^{19}F
- ^{21}Ne
- ^{23}Na
- ^{25}Mg
- ^{27}Al
- ^{29}Si
- ^{31}P
- ^{33}S
- ^{39}K, ^{40}K, ^{41}K
- ^{45}Sc
- ^{47}Ti, ^{49}Ti
- ^{50}V, ^{51}V
- ^{53}Cr
- ^{55}Mn
- ^{57}Fe
- ^{59}Co
- ^{61}Ni
- ^{63}Cu, ^{65}Cu
- ^{67}Zn
- ^{69}Ga, ^{71}Ga
- ^{73}Ge
- ^{77}Se
- ^{81}Br
- ^{87}Rb
- ^{87}Sr
- ^{95}Mo
- ^{109}Ag
- ^{113}Cd
- ^{119}Sn
- ^{125}Te
- ^{127}I
- ^{133}Cs
- ^{135}Ba, ^{137}Ba

- ^{139}La
- ^{183}W
- ^{199}Hg

Applications

Medicine

The use of nuclear magnetic resonance best known to the general public is magnetic resonance imaging for medical diagnosis and MR Microscopy in research settings, however, it is also widely used in chemical studies, notably in NMR spectroscopy such as proton NMR, carbon-13 NMR, deuterium NMR and phosphorus-31 NMR. Biochemical information can also be obtained from living tissue (e.g. human brain tumors) with the technique known as in vivo magnetic resonance spectroscopy or chemical shift NMR Microscopy.

These studies are possible because nuclei are surrounded by orbiting electrons, which are also spinning charged particles such as magnets and, so, will partially shield the nuclei. The amount of shielding depends on the exact local environment. For example, a hydrogen bonded to an oxygen will be shielded differently than a hydrogen bonded to a carbon atom. In addition, two hydrogen nuclei can interact via a process known as spin-spin coupling, if they are on the same molecule, which will split the lines of the spectra in a recognizable way.

Chemistry

By studying the peaks of nuclear magnetic resonance spectra, chemists can determine the structure of many compounds. It can be a very selective technique, distinguishing among many atoms within a molecule or collection of molecules of the same type but which differ only in terms of their local chemical environment. See the articles on carbon-13 NMR and proton NMR for detailed discussions.

By studying T_2*information, a chemist can determine the identity of a compound by comparing the observed nuclear precession frequencies to known frequencies. Further structural data can be elucidated by observing *spin-spin coupling*, a process by which the precession frequency of a nucleus can be influenced by the magnetization transfer from nearby nuclei. Spin-spin coupling is most commonly observed in NMR involving common isotopes, such as Hydrogen-1 (^{1}H NMR).

Because the nuclear magnetic resonance *timescale* is rather slow, compared to other spectroscopic methods, changing the temperature of a T_2*experiment can also give information about fast reactions, such as the Cope rearrangement or about structural dynamics, such as ring-flipping in cyclohexane. At low enough temperatures, a distinction can be made between the axial and equatorial hydrogens in cyclohexane.

An example of nuclear magnetic resonance being used in the determination of a structure is that of buckminsterfullerene (often called "buckyballs", composition C_{60}). This now famous form of carbon has 60 carbon atoms forming a sphere. The carbon atoms are all in identical environments and so should see the same internal H field. Unfortunately, buckminsterfullerene contains no hydrogen and so ^{13}C nuclear magnetic resonance has to be used. ^{13}C spectra require longer acquisition times since carbon-13 is not the common isotope of carbon (unlike hydrogen, where ^{1}H is the common isotope). However, in 1990 the spectrum was obtained by R. Taylor and co-workers at the University of Sussex and was found to contain a single peak, confirming the unusual structure of buckminsterfullerene.[10]

Non-destructive testing

Nuclear magnetic resonance is extremely useful for analyzing samples non-destructively. Radio waves and static magnetic fields easily penetrate many types of matter and anything that is not inherently ferromagnetic. For example, various expensive biological samples, such as nucleic acids, including RNA and DNA, or proteins, can be studied using nuclear magnetic resonance for weeks or months before using destructive biochemical experiments. This also makes nuclear magnetic resonance a good choice for analyzing dangerous samples.

Data acquisition in the petroleum industry

Another use for nuclear magnetic resonance is data acquisition in the petroleum industry for petroleum and natural gas exploration and recovery. A borehole is drilled into rock and sedimentary strata into which nuclear magnetic resonance logging equipment is lowered. Nuclear magnetic resonance analysis of these boreholes is used to measure rock porosity, estimate permeability from pore size distribution and identify pore fluids (water, oil and gas). These instruments are typically low field NMR spectrometers.

Flow probes for NMR spectroscopy

Recently, real-time applications of NMR in liquid media have been developed using specifically designed flow probes (flow cell assemblies)which can replace standard tube probes (Haner and Keifer, 2009). This has enabled techniques that can incorporate the use of high performance liquid chromatography (HPLC) or other continuous flow sample introduction devices. R.L Haner and P.A, Keifer (2009). "Flow Probes for NMR Spectroscopy". *Encyclopedia of Magnetic Resonance*. doi:10.1002/9780470034590.emrstm1085 [11].</ref>

Process control

NMR has now entered the arena of real-time process control and process optimization in oil refineries and petrochemical plants. Two different types of NMR analysis are utilized to provide real time analysis of feeds and products in order to control and optimize unit operations. Time-domain NMR (TD-NMR) spectrometers operating at low field (2–20 MHz for ^{1}H) yield free induction decay data that can be used to determine absolute hydrogen content values, rheological information, and component composition. These spectrometers are used in mining, polymer production, cosmetics and food manufacturing as well as coal analysis. High resolution FT-NMR spectrometers operating in the 60 MHz range with shielded permanent magnet systems yield high resolution ^{1}H NMR spectra of refinery and petrochemical streams. The variation observed in these spectra with changing physical and chemical properties is modeled using chemometrics to yield predictions on unknown samples. The prediction results are provided to control systems via analogue or digital outputs from the spectrometer.

Earth's field NMR

In the Earth's magnetic field, NMR frequencies are in the audio frequency range. Earth's field NMR (EFNMR) is typically stimulated by applying a relatively strong dc magnetic field pulse to the sample and, following the pulse, analyzing the resulting low frequency alternating magnetic field that occurs in the Earth's magnetic field due to free induction decay (FID). These effects are exploited in some types of magnetometers, EFNMR spectrometers, and MRI imagers. Their inexpensive portable nature makes these instruments valuable for field use and for teaching the principles of NMR and MRI.

Quantum computing

NMR quantum computing uses the spin states of molecules as qubits. NMR differs from other implementations of quantum computers in that it uses an ensemble of systems, in this case molecules. The ensemble is initialized to be the thermal equilibrium state (see quantum statistical mechanics).

Magnetometers

Various magnetometers use NMR effects to measure magnetic fields, including proton precession magnetometers (PPM) (also known as proton magnetometers), and Overhauser magnetometers. See also Earth's field NMR.

Makers of NMR equipment

Major NMR instrument makers include Oxford Instruments, Bruker, SpinLock, General Electric, JEOL, Kimble Chase, Philips, Siemens AG, Varian, Inc. and SpinCore Technologies, Inc.

See also

- Carbon-13 NMR
- Chemical shift
- 2D-FT NMRI and spectroscopy
- Dynamic nuclear polarisation (DNP)
- Earth's field NMR (EFNMR)
- Free induction decay (FID)
- In vivo magnetic resonance spectroscopy (MRS)
- J-coupling
- Larmor equation (Not to be confused with Larmor formula).
- Larmor precession
- Low field NMR
- Magic angle spinning
- Magnetometer
- Magnetic resonance imaging (MRI)
- NMR spectra database
- NMR spectroscopy
- NMR Microscopy
- Nuclear magnetic resonance in porous media
- Nuclear quadrupole resonance (NQR)
- Protein dynamics
- Protein NMR
- Proton NMR
- Rabi cycle
- Relaxometry
- Relaxation (NMR)
- Solid-state NMR
- Zero field NMR

References

- G.E Martin, A.S. Zekter (1988). *Two-Dimensional NMR Methods for Establishing Molecular Connectivity*. New York: VCH Publishers. p. 59.
- J.W. Akitt, B.E. Mann (2000). *NMR and Chemistry*. Cheltenham, UK: Stanley Thornes. pp. 273, 287.
- J.P. Hornak. "The Basics of NMR" [12]. Retrieved 2009-02-23.
- J. Keeler (2005). *Understanding NMR Spectroscopy*. John Wiley & Sons. ISBN 0470017864.
- K. Wuthrich (1986). *NMR of Proteins and Nucleic Acids*. New York (NY), USA: Wiley-Interscience.
- J.M Tyszka, S.E Fraser, R.E Jacobs (2005). "Magnetic resonance microscopy: recent advances and applications". *Current Opinion in Biotechnology* **16** (1): 93–99. doi:10.1016/j.copbio.2004.11.004 [13].
- J.C. Edwards. "Principles of NMR" [14]. Process NMR Associates. Retrieved 2009-02-23.
- R.L Haner, P.A. Keifer (2009). *Encyclopedia of Magnetic Resonance*. John Wiley:Chichester. doi:10.1002/9780470034590.emrstm1085 [11].

External links

Tutorial

- NMR/MRI tutorial [15]
- NMR Library [16] NMR Concept

Animations and Simulations

- Animations [17]
- Animation of NMR spin $\frac{1}{2}$ precession [18]
- A free interactive simulation of NMR principles [19]

Software

- CARA [20] - Computer Aided Resonance Assignment, freeware, developed at the group of Prof. Kurt Wüthrich
- CCPN [21] NMR software suite from community led Collaborative Computing Project for NMR.
- Janocchio [22] Conformation-dependent coupling and NOE prediction for small molecules.
- Mnova [23] - Multiplatform NMR processing, analysis and prediction software from Mestrelab Research [24].
- NMR processing software from ACD/Labs [25] for 1D [26] and 2D [27] NMR spectra. DB interface available.
- NMR Prediction software ACD/NMR Predictors [28]
- NMR simulation software QSim [29]
- Free software for simulation of spin coupled multiplets and DNMR spectra WINDNMR-Pro [30]
- NMR processing software NMRPipe [31]
- RMN [32] - An NMR data processing program for the Macintosh.
- SPINUS [33] website that uses neural networks to predict NMR spectra from chemical structures

Video

- introduction to NMR and MRI [34]
- Richard Ernst, NL - Developer of Multdimensional NMR techniques [35] Freeview video provided by the Vega Science Trust.
- 'An Interview with Kurt Wuthrich' [36] Freeview video by the Vega Science Trust (Wüthrich was awarded a Nobel Prize in Chemistry in 2002 "for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution").

Wiki

- NMR Wiki [37] Open NMR,EPR,MRI web project
- NMR wiki in Chinese [38] Chinese NMR, MRI and EPR community

References

[1] I.I. Rabi, J.R. Zacharias, S. Millman, P. Kusch (1938). "A New Method of Measuring Nuclear Magnetic Moment". *Physical Review* **53**: 318. doi: 10.1103/PhysRev.53.318 (http://dx.doi.org/10.1103/PhysRev.53.318).

[2] Filler, Aaron (2009). "The History, Development and Impact of Computed Imaging in Neurological Diagnosis and Neurosurgery: CT, MRI, and DTI". *Nature Precedings*. doi: 10.1038/npre.2009.3267.5 (http://dx.doi.org/10.1038/npre.2009.3267.5).

[3] I.C. Baianu, K.A. Rubinson, J. Patterson (1979). "Ferromagnetic Resonance and Spin Wave Excitations in Metallic Glasses". *J. Phys. Chem. Solids* **40** (12): 941–950. doi: 10.1016/0022-3697(79)90122-7 (http://dx.doi.org/10.1016/0022-3697(79)90122-7).

[4] I.C. Baianu (1979). "Ferromagnetic resonance and spin wave excitations in metallic glasses: The effects of thermal ageing and long-range magnetic ordering". *Solid State Communications* **29**: i–xvi. doi: 10.1016/0038-1098(79)91190-6 (http://dx.doi.org/10.1016/0038-1098(79)91190-6).

[5] Quantum automaton and quantum computation (http://planetphysics.org/encyclopedia/QuantumComputers.html) (see also references therein)

[6] Rabi, I. I. (1938). "A New Method of Measuring Nuclear Magnetic Moment". *Physical Review* **53**: 318. doi: 10.1103/PhysRev.53.318 (http://dx.doi.org/10.1103/PhysRev.53.318).

[7] "Nuclear Magnetic Resonance Fourier Transform Spectroscopy" (http://nobelprize.org/nobel_prizes/chemistry/laureates/1991/ernst-lecture.html)

[8] I.C. Baianu. "Two-dimensional Fourier transforms" (http://planetmath.org/encyclopedia/TwoDimensionalFourierTransforms.html). *2D-FT NMR and MRI*. PlanetMath. . Retrieved 2009-02-22.

[9] Multinuclear NMR (http://chem.ch.huji.ac.il/nmr/techniques/1d/multi.html)

[10] R. Taylor, J.P. Hare, A.K. Abdul-Sada, H.W. Kroto (1990). "Isolation, separation and characterization of the fullerenes C60 and C70: the third form of carbon". *Journal of the Chemical Society, Chemical Communications* **20**: 1423–1425. doi: 10.1039/c39900001423 (http://dx.doi.org/10.1039/c39900001423).

[11] http://dx.doi.org/10.1002%2F9780470034590.emrstm1085

[12] http://www.cis.rit.edu/htbooks/nmr/

[13] http://dx.doi.org/10.1016%2Fj.copbio.2004.11.004

[14] http://www.process-nmr.com/pdfs/NMR%20Overview.pdf

[15] http://www.cis.rit.edu/htbooks/nmr/inside.htm

[16] http://nmr.chinanmr.cn/guide/eNMR/eNMRindex.html

[17] http://www.bigs.de/BLH/en/index.php?option=com_content&view=category&layout=blog&id=51&Itemid=222

[18] http://www.chem.queensu.ca/FACILITIES/NMR/nmr/webcourse/precess.htm

[19] http://vam.anest.ufl.edu/forensic/nmr.html

[20] http://cara.nmr.ch/

[21] http://www.ccpn.ac.uk/

[22] http://janocchio.sourceforge.net

[23] http://mestrelab.com/products/mnova/details.html

[24] http://mestrelab.com/

[25] http://www.acdlabs.com/

[26] http://www.acdlabs.com/products/spec_lab/exp_spectra/nmr/

[27] http://www.acdlabs.com/products/spec_lab/exp_spectra/2d_nmr/

[28] http://www.acdlabs.com/products/spec_lab/predict_nmr/

[29] http://www.bpc.lu.se/QSim

[30] http://www.chem.wisc.edu/areas/reich/plt/windnmr.htm

[31] http://spin.niddk.nih.gov/bax/software/NMRPipe

[32] http://www.grandinetti.org/Software/RMN

[33] http://www2.chemie.uni-erlangen.de/services/spinus/

[34] http://www.youtube.com/watch?v=7aRKAXD4dAg

[35] http://www.vega.org.uk/video/programme/21

[36] http://www.vega.org.uk/video/programme/115

[37] http://www.nmrwiki.org

[38] http://wiki.chinanmr.cn

2D-FT NMRI and spectroscopy

2D-FT Nuclear magnetic resonance imaging (**2D-FT NMRI**), or **two-dimensional Fourier transform** nuclear magnetic resonance imaging (**NMRI**), is primarily a non-invasive imaging technique most commonly used in biomedical research and medical radiology to visualize structures and functions of the living systems and single cells. The physical principle[1] is essentially the same in N(MRI), nuclear magnetic resonance, FT (NMR) spectroscopy, topical NMR, or even in electron spin resonance (ESR); however, the details are significantly different at present for ESR, as only in the early days of NMR the static magnetic field was scanned for obtaining spectra, as it is still the case in many ESR spectrometers. NMRI, on the other hand, often utilizes a linear magnetic field gradient to obtain an image that combines the visualization of molecular structure and dynamics. It is this dynamic aspect of NMRI, as well as its highest sensitivity for the ^{1}H nucleus that distinguishes it very dramatically from X-ray CAT scanning that 'misses' hydrogens because of their very low X-ray scattering factor.

Chemical Shifts

NMR is a very useful family of techniques for chemical and biochemical research because of the chemical shift; this effect consists in a frequency shift of the nuclear magnetic resonance for specific chemical groups or atoms as a result of the partial shielding of the corresponding nuclei from the applied, static external magnetic field by the electron orbitals (or molecular orbitals) surrounding such nuclei present in the chemical groups. Thus, the higher the electron density surrounding a specific nucleus the larger the chemical shift will be. The resulting magnetic field at the

Advanced 3 T clinical diagnostics and biomedical research NMR Imaging instrument.

nucleus is thus lower than the applied external magnetic field and the resonance frequencies observed as a result of such shielding are lower than the value that would be observed in the absence of any electronic orbital shielding. Furthermore, in order to obtain a chemical shift value independent of the strength of the applied magnetic field and allow for the direct comparison of spectra obtained at different magnetic field values, the chemical shift is defined by the ratio of the strength of the local magnetic field value at the observed (electron orbital-shielded) nucleus by the external magnetic field strength, $\mathbf{H}_{loc} / \mathbf{H}_0$. The first NMR observations of the chemical shift, with the correct physical chemistry interpretation, were reported for ^{19}F containing compounds in the early 1950s by Herbert S. Gutowsky and Charles P. Slichter from the University of Illinois at Urbana (USA).

A related effect in metals is called the Knight shift, which is due only to the conduction electrons. Such conduction electrons present in metals induce an "additional" local field at the nuclear site, due to the spin re-orientation of the conduction electrons in the presence of the applied (constant), external magnetic field. This is only broadly `similar' to the chemical shift in either solutions or diamagnetic solids.

Two-dimensional Fourier transform imaging and spectroscopy

2D-FT analysis is a very powerful method for both NMRI and two-dimensional nuclear magnetic resonance spectroscopy (2D-FT NMRS)[2] that allows the three-dimensional reconstruction of polymer and biopolymer structures at atomic resolution[3] for molecular weights (Mw) of dissolved biopolymers in aqueous solutions (for example) up to about 50,000 MW. For larger biopolymers or polymers, more complex methods have been developed to obtain limited structural resolution needed for partial 3D-reconstructions of higher molecular structures, e.g. for up 900,000 MW or even oriented microcrystals in aqueous suspensions or single crystals; such methods have also been reported for *in vivo* 2D-FT NMR spectroscopic studies of algae, bacteria, yeast and certain mammalian cells, including human ones.

2D-FT Definition

A *2D-FT, or two-dimensional Fourier transform*, transforms a function of two temporal variables into a function of two frequency variables. In MRS the frequencies relate to the resonant frequency offsets caused by chemical shift or J-coupling. In MRI a resonance frequency offset is introduced as a function of position; the frequency variables in the Fourier transformed time-data correspond to spatial location in the final image.[4]

Example

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals: $s(t_1,t_2)$ yielding a real 2D-FT NMR `spectrum' (collection of 1D FT-NMR spectra) represented by a matrix $\mathbf{S}$ whose elements are

$$\mathbf{S}\left(\nu_1, \nu_2\right) = \mathbf{Re} \int \int \cos(\nu_1 t_1) \exp^{(-i\nu_2 t_2)} s(t_1, t_2) dt_1 dt_2$$

where ν_1 and ν_2 denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the *covariance matrix* is calculated in the frequency domain according to the following equation

$$\mathbf{C}\left(\nu_2', \nu_2\right) = S^T S = \sum_{\nu^1} [S(\nu_1, \nu_2') S(\nu_1, \nu_2)],$$

with ν_2, ν_2' taking all possible single-quantum frequency values and with the summation carried out over all discrete, double quantum frequencies ν_1.

Brief explanation of NMRI diagnostic uses in Pathology

As an example, a diseased tissue such as a malignant tumor, can be detected by 2D-FT NMRI because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates, and also because of the manner in which a malignant tumor spreads and grows rapidly along the blood vessels adjacent to the tumor, also inducing further vascularization to occur. By changing the pulse delays in the RF pulse sequence employed, and/or the RF pulse sequence itself, one may obtain a `relaxation—based contrast', or contrast enhancement between different types of body tissue, such as normal vs. diseased tissue cells for example.

See also

- Nuclear magnetic resonance (NMR)
- Edward Mills Purcell
- Felix Bloch
- Medical imaging
- Paul C. Lauterbur
- Magnetic resonance microscopy
- Peter Mansfield
- Computed tomography (CT)

- Solid-state NMR
- Knight shift
- John Hasbrouck Van Vleck
- Chemical shift
- Herbert S. Gutowsky
- John S. Waugh
- Charles Pence Slichter
- Protein nuclear magnetic resonance spectroscopy
- Kurt Wüthrich
- Nuclear Overhauser effect
- Fourier transform spectroscopy(FTS)
- Jean Jeneer
- Richard R. Ernst

- FT-NIRS (NIR)
- Magnetic resonance elastography

- Relaxation
- Earth's field NMR (EFNMR)
- Robinson oscillator

Further Reading

- Antoine Abragam. 1968. *Principles of Nuclear Magnetic Resonance.*, 895 pp., Cambridge University Press: Cambridge, UK.
- Charles P. Slichter.1996. *Principles of Magnetic Resonance.* Springer: Berlin and New York, Third Edition., 651pp. ISBN 0-387-50157-6.
- Kurt Wüthrich. 1986, *NMR of Proteins and Nucleic Acids.*, J. Wiley and Sons: New York, Chichester, Brisbane, Toronto, Singapore. (Nobel Laureate in 2002 for 2D-FT NMR Studies of Structure and Function of Biological Macromolecules [5]
- Protein structure determination in solution by NMR spectroscopy [6] Kurt Wüthrich. J Biol Chem. 1990 December 25;265(36):22059-62
- Richard R. Ernst. 1992. Nuclear Magnetic Resonance Fourier Transform (2D-FT) Spectroscopy. Nobel Lecture [7], on December 9, 1992.
- Peter Mansfield. 2003.Nobel Laureate in Physiology and Medicine for (2D and 3D) MRI [8]
- D. Benett. 2007. PhD Thesis. Worcester Polytechnic Institute. PDF of 2D-FT Imaging Applications to NMRI in Medical Research. [9] Worcester Polytechnic Institute. (Includes many 2D-FT NMR images of human brains.)
- Paul Lauterbur. 2003.Nobel Laureate in Physiology and Medicine for (2D and 3D) MRI. [10]
- Jean Jeener. 1971. Two-dimensional Fourier Transform NMR, presented at an Ampere International Summer School, Basko Polje, unpublished. A verbatim quote follows from Richard R. Ernst's Nobel Laureate Lecture delivered on December 2, 1992, "A new approach to measure two-dimensional (2D) spectra." has been proposed by Jean Jeener at an Ampere Summer School in Basko Polje, Yugoslavia, 1971 (Jean Jeneer,1971)). He suggested a 2D Fourier transform experiment consisting of two $\pi/2$ pulses with a variable time t_1 between the pulses and the time variable t_2 measuring the time elapsed after the second pulse as shown in Fig. 6 that expands the principles of Fig. 1. Measuring the response $s(t_1,t_2)$ of the two-pulse sequence and Fourier-transformation with respect to both time variables produces a two-dimensional spectrum $S(O_1,O_2)$ of the desired form. This two-pulse experiment by Jean Jeener is the forefather of a whole class of $2D$ experiments that can also easily be expanded to multidimensional spectroscopy.

- Dudley, Robert, L (1993). "High-Field NMR Instrumentation". *Ch. 10 in Physical Chemistry of Food Processes* (New York: Van Nostrand-Reinhold) **2**: 421−30. ISBN 0-442-00582-2.

- Baianu, I.C.; Kumosinski, Thomas (August 1993). "NMR Principles and Applications to Structure and Hydration,". *Ch.9 in Physical Chemistry of Food Processes* (New York: Van Nostrand-Reinhold) **2**: 338−420. ISBN 0-442-00582-2.

- Haacke, E Mark; Brown, Robert F; Thompson, Michael; Venkatesan, Ramesh (1999). *Magnetic resonance imaging: physical principles and sequence design*. New York: J. Wiley & Sons. ISBN 0-471-35128-8.

- Raftery D (August 2006). "MRI without the magnet" [11]. *Proc Natl Acad Sci USA*. **103** (34): 12657−8. doi:10.1073/pnas.0605625103 [12]. PMID 16912110 [13].

- Wu Y, Chesler DA, Glimcher MJ, *et al.* (February 1999). "Multinuclear solid-state three-dimensional MRI of bone and synthetic calcium phosphates" [14]. *Proc. Natl. Acad. Sci. U.S.A.* **96** (4): 1574−8. doi:10.1073/pnas.96.4.1574 [15]. PMID 9990066 [16]. PMC 15521 [17].

External links

- Cardiac Infarct or "heart attack" Imaged in Real Time by 2D-FT NMRI [18]
- Interactive Flash Animation on MRI [19] - *Online Magnetic Resonance Imaging physics and technique course*
- Herbert S. Gutowsky
- Jiri Jonas and Charles P. Slichter: NMR Memoires at [[NAS [20]] about Herbert Sander Gutowsky; NAS = National Academy of Sciences, USA,]
- 3D Animation Movie about MRI Exam [21]
- International Society for Magnetic Resonance in Medicine [22]
- Danger of objects flying into the scanner [23]

Related Wikipedia websites

- Medical imaging
- Computed tomography
- Magnetic resonance microscopy
- Fourier transform spectroscopy
- FT-NIRS
- Chemical imaging
- Magnetic resonance elastography
- Nuclear magnetic resonance (NMR)
- Chemical shift
- Relaxation
- Robinson oscillator
- Earth's field NMR (EFNMR)
- Rabi cycle

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References

[1] Abragam, Antoine (1968). *Principles of Nuclear Magnetic Resonance*. Cambridge, UK: Cambridge University Press. ISBN 019852014X.

[2] Ernst, Richard R. (9 December 1992). Nobel Lecture "Nuclear Magnetic Resonance Fourier Transform (2D-FT) Spectroscopy" (http:// nobelprize.org/nobel_prizes/chemistry/laureates/1991/ernst-lecture.pdf). Nodel Foundation. Nobel Lecture. Retrieved 29 November 2009.

[3] http://en.wikipedia.org/wiki/Nuclear_magnetic_resonance#Nuclear_spin_and_magnets Kurt Wüthrich in 1982-1986 : 2D-FT NMR of solutions

[4] Slichter, Charles P. (1996). *Principles of Magnetic Resonance, Third Edition*. Berlin and New York: Springer. ISBN 0-387-50157-6.

[5] http://nobelprize.org/nobel_prizes/chemistry/laureates/2002/wutrich-lecture.pdf

[6] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2266107&query_hl=33& itool=pubmed_docsum

[7] http://nobelprize.org/nobel_prizes/chemistry/laureates/1991/ernst-lecture.pdf

[8] http://nobelprize.org/nobel_prizes/medicine/laureates/2003/mansfield-lecture.html

[9] http://www.wpi.edu/Pubs/ETD/Available/etd-081707-080430/unrestricted/dbennett.pdf

[10] http://nobelprize.org/nobel_prizes/medicine/laureates/2003/lauterbur-lecture.html

[11] http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1568902

[12] http://dx.doi.org/10.1073%2Fpnas.0605625103

[13] http://www.ncbi.nlm.nih.gov/pubmed/16912110

[14] http://www.pnas.org/cgi/pmidlookup?view=long&pmid=9990066

[15] http://dx.doi.org/10.1073%2Fpnas.96.4.1574

[16] http://www.ncbi.nlm.nih.gov/pubmed/9990066

[17] http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=15521

[18] http://www.mr-tip.com/exam_gifs/cardiac_infarct_short_axis_cine_6.gif

[19] http://www.e-mri.org

[20] http://books.nap.edu/html/biomems/hgutowsky.pdf

[21] http://www.patiencys.com/MRI/

[22] http://www.ismrm.org

[23] http://www.simplyphysics.com/flying_objects.html

[24] http://planetphysics.org/encyclopedia/2DFTImaging.html

[25] http://planetphysics.org/

Vibrational circular dichroism

Vibrational circular dichroism (VCD) is a spectroscopic technique which detects differences in attenuation of left and right circularly polarized light passing through a sample. It is basically circular dichroism spectroscopy in the infrared and near infrared ranges[1] .

Because VCD is sensitive to the mutual orientation of distinct groups in a molecule, it provides three-dimensional structural information. Thus, it is a powerful technique as VCD spectra of enantiomers can be simulated using *ab initio* calculations, thereby allowing the identification of absolute configurations of small molecules in solution from VCD spectra. Among such quantum computations of VCD spectra resulting from the chiral properties of small organic molecules are those based on density functional theory (DFT) and gauge-invariant atomic orbitals (GIAO). As a simple example of the experimental results that were obtained by VCD are the spectral data obtained within the carbon-hydrogen (C-H) stretching region of 21 amino acids in heavy water solutions. Measurements of vibrational optical activity (VOA) have thus numerous applications, not only for small molecules, but also for large and complex biopolymers such as muscle proteins (myosin, for example) and DNA.

Vibrational modes
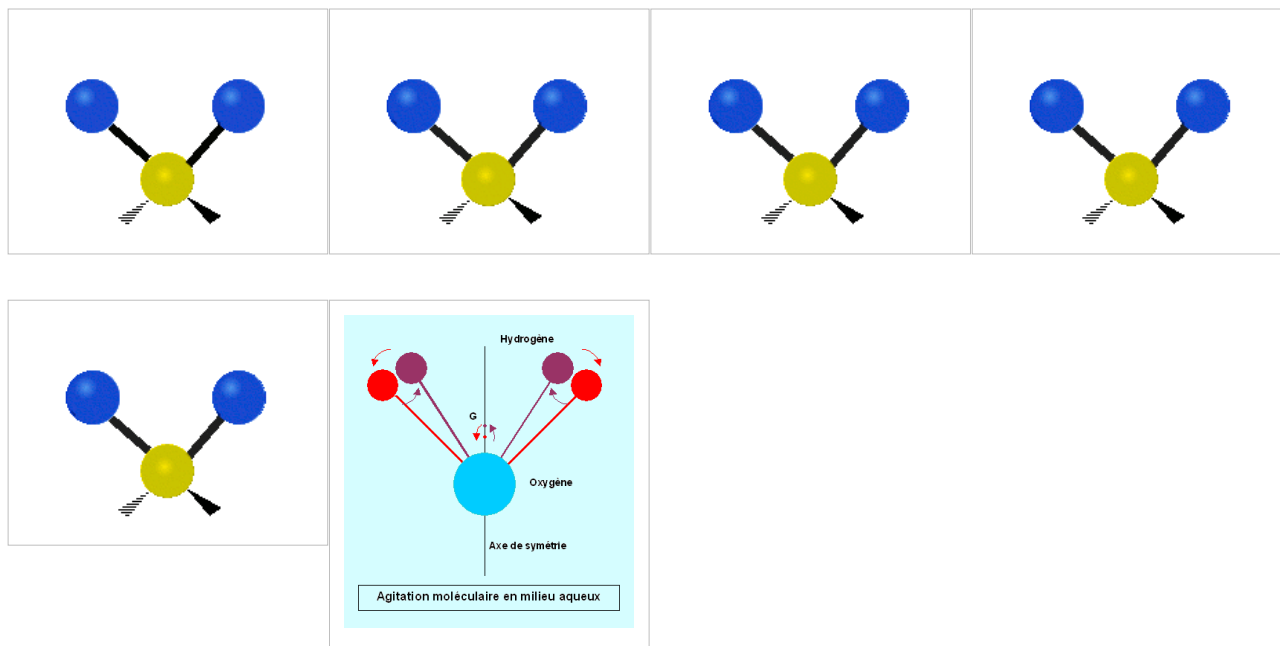
Theory of VCD

While the fundamental quantity associated with the infrared absorption is the dipole strength, the differential absorption is proportional also to the rotational strength, a quantity which depends on both the electric and magnetic dipole transition moments. Sensitivity of the handedness of a molecule toward circularly polarized light results from the form of the rotational strength.

VCD of peptides and proteins

Extensive VCD studies have been reported for both polypeptides and several proteins in solution[2] [3] [4] ; several recent reviews were also compiled[5] [6] [7] [8] . An extensive but not comprehensive VCD publications list is also provided in the "References" section. The published reports over the last 22 years have established VCD as a powerful technique with improved results over those previously obtained by visible/UV circular dichroism (CD) or

optical rotatory dispersion (ORD) for proteins and nucleic acids.

Amino acid and polypeptide structures
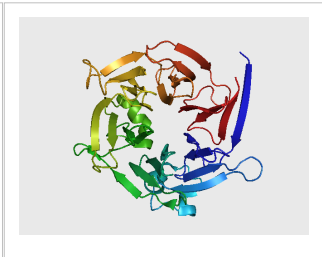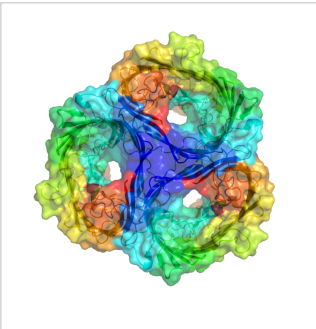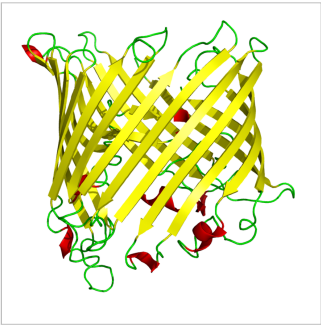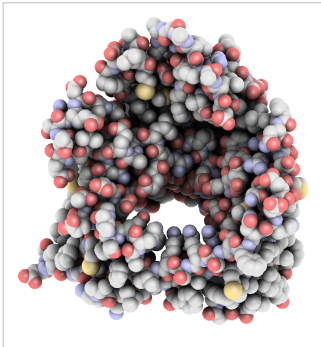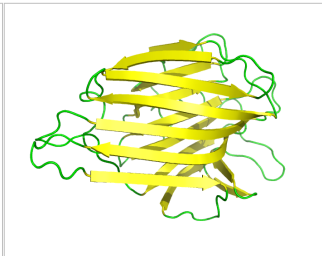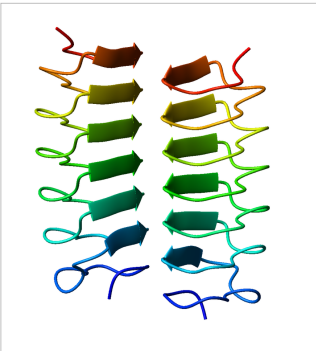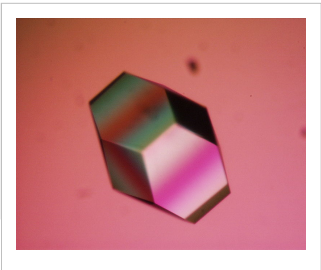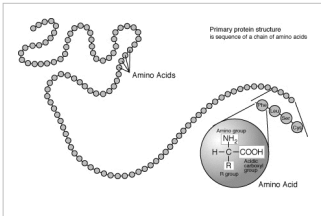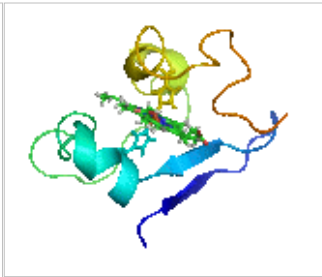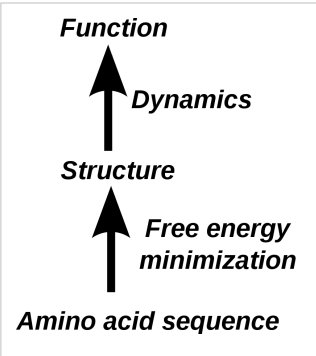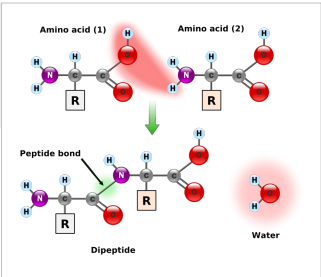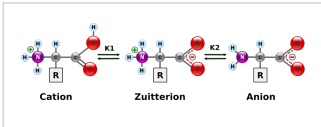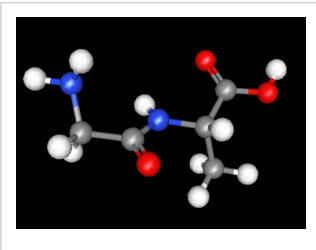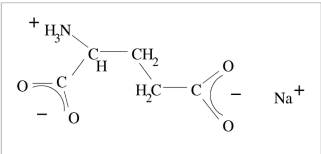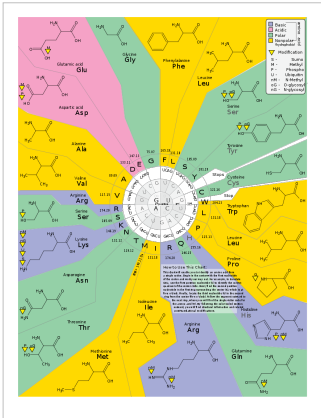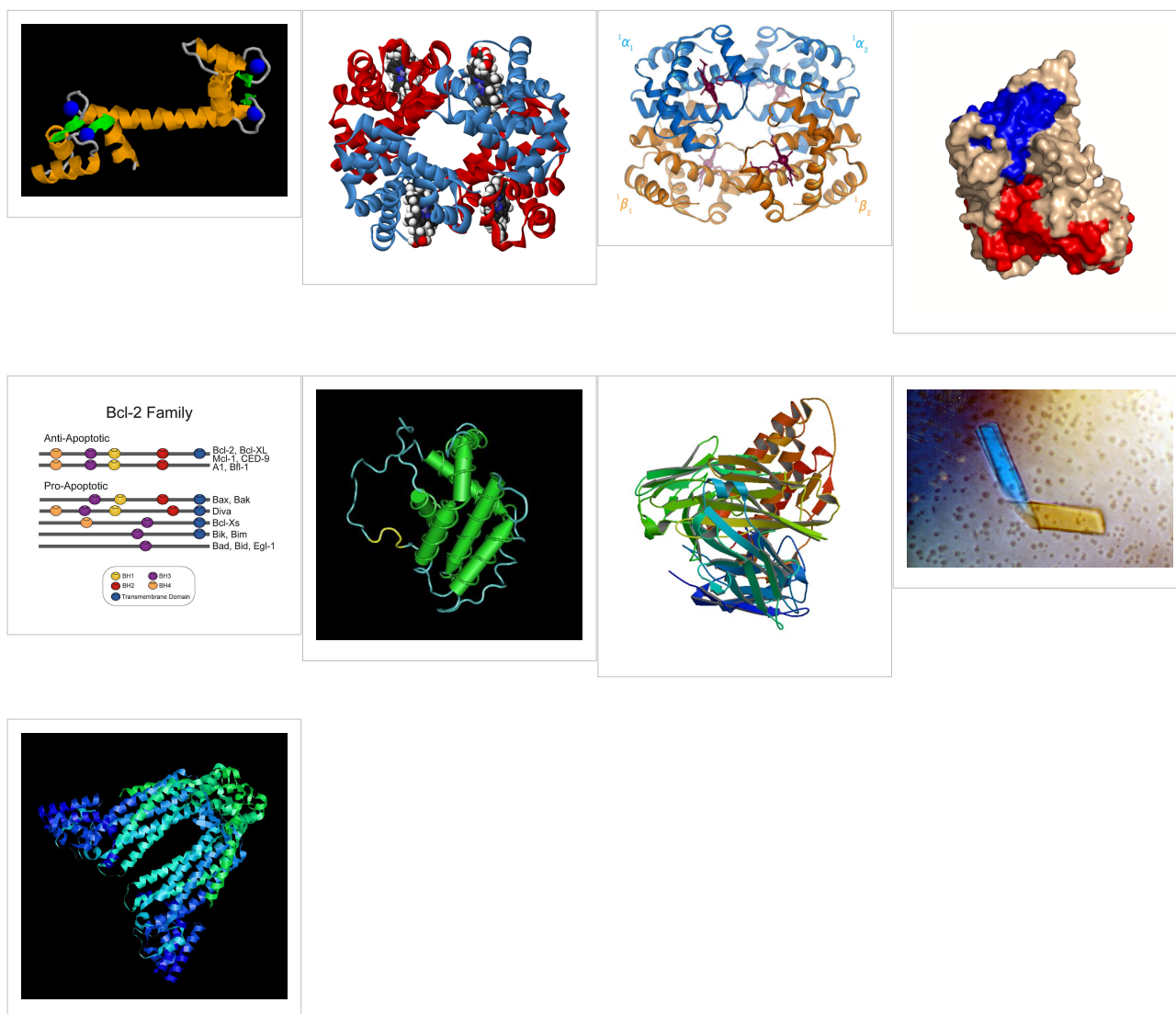
VCD of nucleic acids

VCD spectra of nucleotides, synthetic polynucleotides and several nucleic acids, including DNA, have been reported and assigned in terms of the type and number of helices present in A-, B-, and Z- DNA.

VCD Instrumentation

For biopolymers such as proteins and nucleic acids, the difference in absorbance between the levo- and dextro-configurations is five orders of magnitude smaller than the corresonding (unpolarized) absorbance. Therefore, VCD of biopolymers requires the use of very sensitive, specially built instrumentation as well as time-averaging over relatively long intervals of time even with such sensitive VCD spectrometers. Most CD instruments produce left- and right- circularly polarized light which is then either sine-wave or square-wave modulated, with subsequent phase-sensitive detection and lock-in amplification of the detected signal. In the case of FT-VCD, a photo-elastic modulator (PEM) is employed in conjunction with an FT-IR interferometer set-up. An example is that of a Bomem model MB-100 FT-IR interferometer equipped with additional polarizing optics/ accessories needed for recording VCD spectra. A parallel beam emerges through a side port of the interferometer which passes first through a wire grid linear polarizer and then through an octagonal-shaped ZnSe crystal PEM which modulates the polarized beam at a fixed, lower frequency such as 37.5 kHz. A mechanically stressed crystal such as ZnSe exhibits birefringence when stressed by an adjacent piezoelectric transducer. The linear polarizer is positioned close to, and at 45 degrees, with

respect to the ZnSe crystal axis. The polarized radiation focused onto the detector is doubly modulated, both by the PEM and by the interferometer setup. A very low noise detector, such as MCT (HgCdTe), is also selected for the VCD signal phase-sensitive detection. Quasi-complete commercial FT-VCD instruments are also available from a few manufacturers but these are quite expensive and also have to be still considered as being at the prototype stage. To prevent detector saturation an appropriate, long wave pass filter is placed before the very low noise MCT detector, which allows only radiation below 1750 cm^{-1} to reach the MCT detector; the latter however measures radiation only down to 750 cm^{-1}. FT-VCD spectra accumulation of the selected sample solution is then carried out, digitized and stored by an in-line computer. Published reviews that compare various VCD methods are also available.[9] [10]
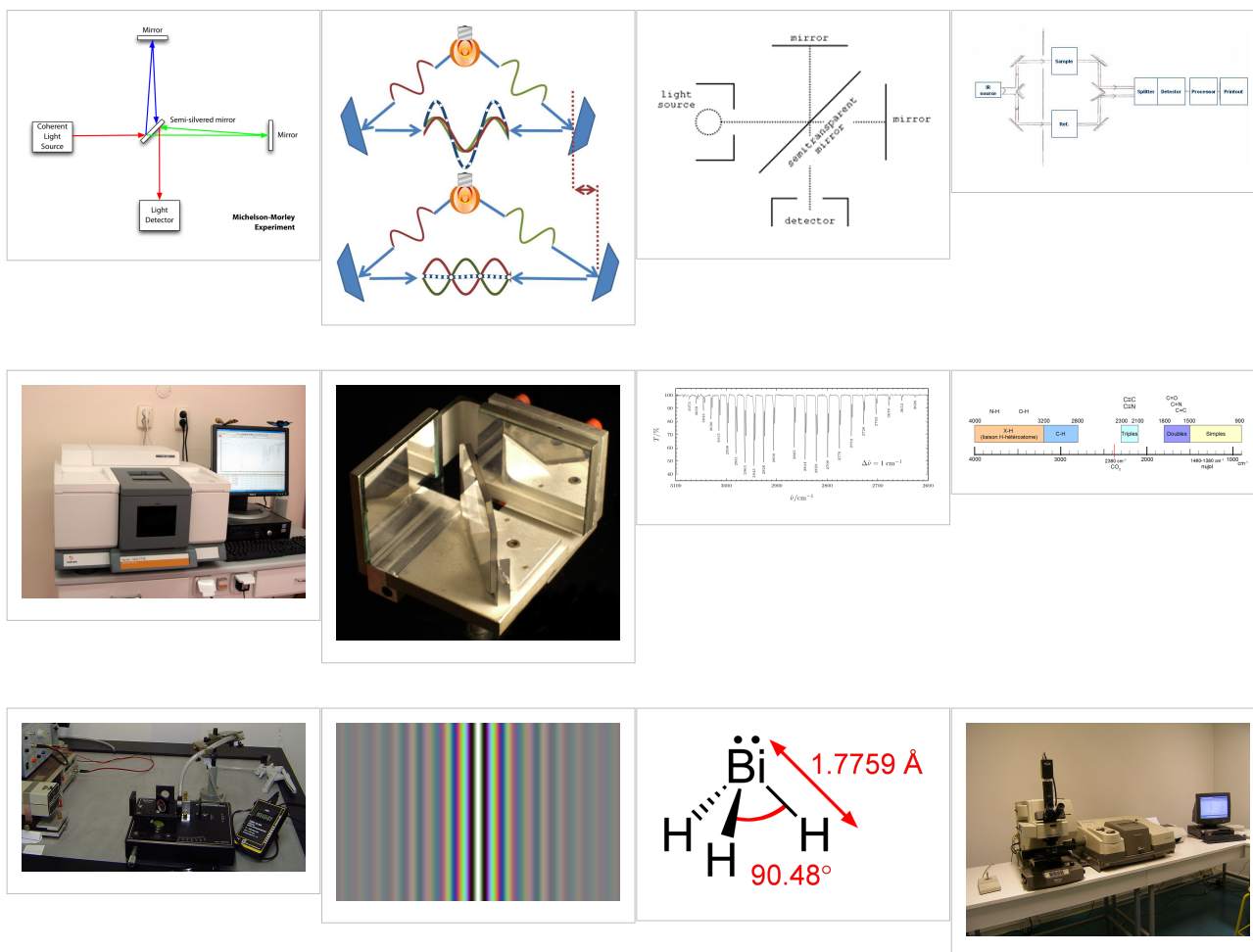
Magnetic VCD

VCD spectra have also been reported in the presence of an applied external magnetic field[11] . This method can enhance the VCD spectral resolution for small molecules[12] [13] [14] [15] [16] .

Raman optical activity (ROA)

ROA is a technique complementary to VCD especially useful in the 50—1600 cm^{-1} spectral region; it is considered as the technique of choice for determining optical activity for photon energies less than 600 cm^{-1}.

References

Peptides and proteins

- Huang R, Wu L, McElheny D, Bour P, Roy A, Keiderling TA. Cross-Strand Coupling and Site-Specific Unfolding Thermodynamics of a Trpzip beta-Hairpin Peptide Using (13)C Isotopic Labeling and IR Spectroscopy. *The journal of physical chemistry. B*. 2009 Apr;113(16):5661-74.
- "Vibrational Circular Dichroism of Poly alpha-Benzyl-L-Glutamate," R. D. Singh, and T. A. Keiderling, Biopolymers, 20, 237-40 (1981).
- "Vibrational Circular Dichroism of Polypeptides II. Solution Amide II and Deuteration Results," A. C. Sen and T. A. Keiderling, Biopolymers, 23, 1519-32 (1984).
- "Vibrational Circular Dichroism of Polypeptides III. Film Studies of Several alpha-Helical and ß-Sheet Polypeptides," A. C. Sen and T. A. Keiderling, Biopolymers, 23, 1533-46 (1984).
- "Vibrational Circular Dichroism of Polypeptides IV. Film Studies of L-Alanine Homo Oligopeptides," U. Narayanan, T. A. Keiderling, G. M. Bonora, and C. Toniolo, *Biopolymers* 24, 1257-63 (1985).
- "Vibrational Circular Dichroism of Polypeptides, T. A. Keiderling, S. C. Yasui, A. C. Sen, C. Toniolo, G. M. Bonora, in Peptides Structure and Function, Proceedings of the 9th American Peptide Symposium," ed. C. M. Deber, K. Kopple, V. Hruby; Pie rce Chemical: Rockford, IL; 167-172 (1985).
- "Vibrational Circular Dichroism of Polypeptides V. A Study of 310 Helical-Octapeptides" S. C. Yasui, T. A. Keiderling, G. M. Bonora, C. Toniolo, Biopolymers 25, 79-89 (1986).
- "Vibrational Circular Dichroism of Polypeptides VI. Polytyrosine alpha-helical and Random Coil Results," S. C. Yasui and T. A. Keiderling, Biopolymers 25, 5-15 (1986).
- "Vibrational Circular Dichroism of Polypeptides VII. Film and Solution Studies of alpha-forming Homo-Oligopeptides," U. Narayanan, T. A. Keiderling, G. M. Bonora, C. Toniolo, *Journal of the American Chemical Society*, 108, 2431-2437 (1986).
- "Vibrational Circular Dichroism of Polypeptides VIII. Poly Lysine Conformations as a Function of pH in Aqueous Solution," S. C. Yasui, T. A. Keiderling, Journal of the American Chemical Society, 108, 5576-5581 (1986).
- "Vibrational Circular Dichroism of Polypeptides IX. A Study of Chain Length Dependence for 310-Helix Formation in Solution." S. C. Yasui, T. A. Keiderling, F. Formaggio, G. M. Bonora, C. Toniolo, Journal of the American Chemical Society 108, 4988-499 3 (1986).
- "Vibrational Circular Dichroism of Biopolymers." T. A. Keiderling, *Nature*, 322, 851-852 (1986).
- "Vibrational Circular Dichroism of Polypeptides X. A Study of alpha-Helical Oligopeptides in Solution." S. C. Yasui, T. A. Keiderling, R. Katachai, Biopolymers 26, 1407-1412 (1987).
- "Vibrational Circular Dichroism of Polypeptides XI. Conformation of Poly(L-Lysine(Z)-L-Lysine(Z)-L-1-Pyrenylalanine) and Poly(L-Lysine(Z)-L-Lysine(Z)-L-1-Napthylala-nine) in Solution" S. C. Yasui, T. A. Keiderling, and M. Sisido, *Macromolecules* 20, 2 403-2406 (1987).
- "Vibrational Circular Dichroism of Biopolymers" T. A. Keiderling, S. C. Yasui, A. C. Sen, U. Narayanan, A. Annamalai, P. Malon, R. Kobrinskaya, L. Yang, in "F.E.C.S. Second International Conference on Circular

Dichroism, Conference Proceedings," ed. M. Kajtar, L. Eötvös Univ., Budapest, 1987, p. 155-161.

- "Vibrational Circular Dichroism of Poly-L-Proline and Other Helical Poly-peptides," R. Kobrinskaya, S. C. Yasui, T. A. Keiderling, in "Peptides: Chemistry and Biology, Proceedings of the 10th American Peptide Symposium," ed. G. R. Marshall, ESCOM, L eiden, 1988, p. 65-67.

- "Vibrational Circular Dichroism of Polypeptides with Aromatic Side Chains," S. C. Yasui, T. A. Keiderling, in "Peptides: Chemistry and Biology, Proceedings of the 10th American Peptide Symposium," ed. G. R. Marshall, ESCOM, Leiden, 1988, p. 90-92.

- "Vibrational Circular Dichroism of Polypeptides XII. Re-evaluation of the Fourier Transform Vibrational Circular Dichroism of Poly-gamma-Benzyl-L-Glutamate," P. Malon, R. Kobrinskaya, T. A. Keiderling, Biopolymers 27, 733-746 (1988).

- "Vibrational Circular Dichroism of Biopolymers," T. A. Keiderling, S. C. Yasui, U. Narayanan, A. Annamalai, P. Malon, R. Kobrinskaya, L. Yang, in *Spectroscopy of Biological Molecules New Advances* ed. E. D. Schmid, F. W. Schneider, F. Siebert, p. 73-76 (1988).

- "Vibrational Circular Dichroism of Polypeptides and Proteins," S. C. Yasui, T. A. Keiderling, *Mikrochimica Acta*, II, 325-327, (1988).

- "(1R,7R)-7-Methyl-6,9,-Diazatricyclo[6,3,0,01,6]Tridecanne-5,10-Dione, A Tricyclic Spirodilactam Containing Non-planar Amide Groups: Synthesis, NMR, Crystal Structure, Absolute Configuration, Electronic and Vibrational Circular Dichroism" P. Malon, C . L. Barness, M. Budesinsky, R. K. Dukor, D. van der Helm, T. A. Keiderling, Z. Koblicova, F. Pavlikova, M. Tichy, K. Blaha, Collections of Czechoslovak Chemical Communications 53, 2447-2472 (1988).

- "Vibrational Circular Dichroism of Poly Glutamic Acid" R. K. Dukor, T. A. Keiderling, in *Peptides 1988* (ed. G. Jung, E. Bayer) Walter de Gruyter, Berlin (1989) pp 519–521.

- "Biopolymer Conformational Studies with Vibrational Circular Dichroism" T. A. Keiderling, S. C. Yasui, P. Pancoska, R. K. Dukor, L. Yang, SPIE Proceeding 1057, ("Biomolecular Spectroscopy," ed. H. H. Mantsch, R. R. Birge) 7-14 (1989).

- "Vibrational Circular Dichroism. Comparison of Techniques and Practical Considerations" T. A. Keiderling, in "Practical Fourier Transform Infrared Spectroscopy. Industrial and Laboratory Chemical Analysis," ed. J. R. Ferraro, K. Krishnan (Academic Press, San Diego, 1990) p. 203-284.

- "Vibrational Circular Dichroism Study of Unblocked Proline Oligomers," R. K. Dukor, T. A. Keiderling, V. Gut, *International Journal of Peptide and Protein Research*, 38, 198-203 (1991).

- "Reassessment of the Random Coil Conformation. Vibrational CD Study of Proline Oligopeptides and Related Polypeptides" R. K. Dukor and T. A. Keiderling, Biopolymers 31 1747-1761 (1991).

- "Vibrational CD of the Amide II band in Some Model Polypeptides and Proteins" V. P. Gupta, T. A. Keiderling, Biopolymers 32 239-248 (1992).

- "Vibrational Circular Dichroism of Proteins Polysaccharides and Nucleic Acids" T. A. Keiderling, Chapter 8 in *Physical Chemistry of Food Processes, Vol. 2 Advanced Techniques, Structures and Applications.*, eds. I.C. Baianu, H. Pessen, T. Kumosinski, Van Norstrand—Reinhold, New York (1993), pp 307–337.

- "Structural Studies of Biological Macromolecules using Vibrational Circular Dichroism" T. A. Keiderling, P. Pancoska, Chapter 6 in Advances in Spectroscopy Vol. 21, *Biomolecular Spectroscopy Part B* eds. R. E. Hester, R. J. H. Clarke, John W iley Chichester (1993) pp 267–315.

- "Ab Initio Simulations of the Vibrational Circular Dichroism of Coupled Peptides" P. Bour and T. A. Keiderling, Journal of the American Chemical Society 115 9602-9607 (1993).

- "Ab initio Simulations of Coupled Peptide Vibrational Circular Dichroism" P. Bour, T. A. Keiderling in "Fifth International Conference on The Spectroscopy of Biological Molecules" Th. Theophanides, J. Anastassopoulou, N. Fotopoulos (Eds), Kluwen Aca demic Publ., Dortrecht, 1993, p. 29-30.

- "Vibrational Circular Dichroism Spectroscopy of Peptides and Proteins" T. A. Keiderling, in "Circular Dichroism Interpretations and Applications," K. Nakanishi, N. Berova, R. Woody, Eds., VCH Publishers, New York, (1994)

pp 497–521.

- "Conformational Study of Sequential Lys-Leu Based Polymers and Oligomers using Vibrational and Electronic Circular Dichroism Spectra" V. Baumruk, D. Huo, R. K. Dukor, T. A. Keiderling, D. LeLeivre and A. Brack Biopolymers 34, 1115-1121 (1994).

- "Vibrational Optical Activity of Oligopeptides" T. B. Freedman, L. A. Nafie, T. A. Keiderling *Biopolymers* (Peptide Science) 37 (ed. C. Toniolo) 265-279 (1995).

- "Characterization of ß-bend ribbon spiral forming peptides using electronic and vibrational circular dichroism" G. Yoder, T. A. Keiderling, F. Formaggio, M. Crisma, C. Toniolo Biopolymers 35, 103-111 (1995).

- "Vibrational Circular Dichroism as a Tool for Determination of Peptide Secondary Structure" P. Bour, T. A. Keiderling, P. Malon, in "Peptides 1994 (Proceedings of the 23rd European Peptide Symposium,1994," (H.L.S. Maia, ed.), Escom, Le iden 1995, p. 517-518.

- "Helical Screw Sense of homo-oligopeptides of C-alpha-methylated alpha-amino acids as Determined with Vibrational Circular Dichroism." G. Yoder, T. A. Keiderling, M. Crisma, F. Formaggio, C. Toniolo, J. Kamphuis, Tetrahedron Asymmetry 6, 687 -690 (1995).

- "Conformational Study of Linear Alternating and Mixed D- and L-Proline Oligomers Using Electronic and Vibrational CD and Fourier Transform IR." W. M&#228stle, R. K. Dukor, G. Yoder, T. A. Keiderling *Biopolymers* 36, 623-631 (1995).

- Review: "Vibrational Circular Dichroism Applications to Conformational Analysis of Biomolecules" T. A. Keiderling in *Circular Dichroism and the Conformational Analysis of Biomolecules* ed. G. D. Fasman, Plenum, New York (1996) p. 555-585.

- "Mutarotation studies of Poly L-Proline using FT-IR, Electronic and Vibrational Circular Dichroism" R. K. Dukor, T. A. Keiderling, Biospectroscopy 2, 83-100 (1996).

- "Vibrational Circular Dichroism Applications in Proteins and Peptides" T. A. Keiderling, Proceedings of the NATO ASI in Biomolecular Structure and Dynamics, Loutrakii Greece, May 1996, Ed. G. Vergoten (delayed second volume to 1998).

- "Transfer of Molecular Property Tensors in Cartesian Coordinates: A new algorithm for simulation of vibrational spectra" Petr Bour, Jana Sopkova, Lucie Bednarova, Petr Malon, T. A. Keiderling, *Journal of Computational Chemistry* 18, 6 46-659 (1997).

- "Vibrational Circular Dichroism Characterization of Alanine-Rich Peptides." Gorm Yoder and Timothy A. Keiderling, "Spectroscopy of Biological Molecules: Modern Trends," Ed. P. Carmona, R. Navarro, A. Hernanz, Kluwer Acad. Pub., Netherlands (1997) p p. 27-28.

- "Ionic strength effect on the thermal unfolding of alpha-spectrin peptides." D. Lusitani, N. Menhart, T.A. Keiderling and L. W. M. Fung. *Biochemistry* 37(1998)16546-16554.

- "In search of the earliest events of hCGb folding: structural studies of the 60-87 peptide fragment" S. Sherman, L. Kirnarsky, O. Prakash, H. M. Rogers, R.A.G.D. Silva, T.A. Keiderling, D. Smith, A.M. Hanly, F. Perini, and R.W. Ruddon, American Pep tide Symposium Proceedings, 1997.

- "Cold Denaturation Studies of (LKELPKEL)n Peptide Using Vibrational Circular Dichroism and FT-IR". R. A. G. D. Silva, Vladimir Baumruk, Petr Pancoska, T. A. Keiderling, Eric Lacassie, and Yves Trudelle, American Peptide Symposium Proceedings, 1997.

- "Simulations of oligopeptide vibrational CD. Effects of isotopic labeling." Petr Bour, Jan Kubelka,T. A. Keiderling Biopolymers 53, 380-395 (2000).

- "Site specific conformational determination in thermal unfolding studies of helical peptides using vibrational circular dichroism with isotopic substitution" R. A. G. D. Silva, Jan Kubelka, Petr Bour, Sean M. Decatur, Timothy A. Keiderling, *Proceedings of the National Academy of Sciences* (PNAS:USA) 97, 8318-8323 (2000).

- "Folding studies on the human chorionic gonadotropin b -subunit using optical spectroscopy of peptide fragments" R. A. G. D. Silva, S. A. Sherman, F. Perini, E. Bedows, T. A. Keiderling, Journal of the American Chemical Society, 122, 8623-8630 (2000).

- "Peptide and Protein Conformational Studies with Vibrational Circular Dichroism and Related Spectroscopies", Timothy A. Keiderling, (Revised and Expanded Chapter) In Circular Dichroism: Principles and Applications, 2nd Edition. (Eds. K. Nakanishi, N. Berova and R. A. Woody, John Wiley & Sons, New York (2000) p. 621-666.

- "Conformation studies with Optical Spectroscopy of peptides taken from hairpin sequences in the Human Chorionic Gonadotropin " R. A. G. D. Silva, S. A. Sherman, E. Bedows, T. A. Keiderling, Peptides for the New Millenium, Proceedings of the 16th American Peptide Symposium, (June, 1999 Minneapolis, MN) Ed.G. B. Fields, J. P. Tam, G. Barany, Kluwer Acad. Pub., Dordrecht,(2000) p. 325-326.

- "Analysis of Local Conformation within Helical Peptides via Isotope-Edited Vibrational Spectroscopy." S. M. Decatur, T. A. Keiderling, R. A. G. D.Silva, and P. Bour, Peptides for the New Millenium, Proceedings of the 16th American Peptide Symposium, (June, 1999 Minneapolis, MN) Ed. Ed.G. B. Fields, J. P. Tam, G. Barany, Kluwer Acad. Pub., Dordrecht, (2000) p. 414-416.

- "The anomalous infrared amide I intensity distribution in C-13 isotopically labeled peptide beta-sheets comes from extended, multiple stranded structures. An *Ab Initio* study." Jan Kubelka and T. A. Keiderling , *Journal of the American Chemical Society.* 123, 6142-6150 (2001).

- "Vibrational Circular Dichroism of Peptides and Proteins: Survey of Techniques, Qualitative and Quantitative Analyses, and Applications" Timothy A. Keiderling, Chapter in Infrared and Raman Spectroscopy of Biological Materials, Ed. Bing Yan and H.-U. Gremlich, Marcel Dekker, New York (2001) p. 55-100.

- "Chirality in peptide vibrations. Ab initio computational studies of length, solvation, hydrogen bond, dipole coupling and isotope effects on vibrational CD. " Jan Kubelka, Petr Bour, R. A. Gangani D. Silva, Sean M. Decatur, Timothy A. Keiderling, ACS Symposium Series 810, ["Chirality: Physical Chemistry," (Ed. Janice Hicks) American Chemical Society, Washington, DC] (2002), pp. 50–64.

- "Spectroscopic Characterization of Selected b-Sheet Hairpin Models", J. Hilario, J. Kubelka, F. A. Syud, S. H. Gellman, and T. A. Keiderling. Biopolymers (Biospectroscopy) 67: 233-236 (2002)

- " Discrimination between peptide 3_{10}- and alpha-helices. Theoretical analysis of the impact of alpha-methyl substitution on experimental spectra " Jan Kubelka, R. A. Gangani D. Silva, and T. A. Keiderling, *Journal of the American Chemical Society*, 124, 5325-5332 (2002).

- "*Ab Initio* Quantum Mechanical Models of Peptide Helices and their Vibrational Spectra" Petr Bour, Jan Kubelka and T. A. Keiderling, Biopolymers 65, 45-59 (2002).

- "Discriminating 3_{10}- from alpha-helices. Vibrational and electronic CD and IR Absorption study of related Aib-contining oligopeptides" R. A. Gangani D. Silva, Sritana Yasui, Jan Kubelka, Fernando Formaggio, Marco Crisma, Claudio Toniolo, and Timothy A. Keiderling, Biopolymers 65, 229-243 (2002).

- "Spectroscopic characterization of Unfolded peptides and proteins studied with infrared absorption and vibrational circular dichroism spectra" T. A. Keiderling and Qi Xu, Advances in Protein Chemistry Volume 62, [Unfolded Proteins, Dedicated to John Edsall, Ed.: George Rose, Academic Press:New York] (2002), pp. 111–161.

- "Protein and Peptide Secondary Structure and Conformational Determination with Vibrational Circular Dichroism " Timothy A. Keiderling, *Current Opinions in Chemical Biology* (Ed. Julie Leary and Mark Arnold) 6, 682-688 (2002).

- Review: Conformational Studies of Peptides with Infrared Techniques. Timothy A. Keiderling and R. A. G. D. Silva, in Synthesis of Peptides and Peptidomimetics, Ed. M. Goodman and G. Herrman, Houben-Weyl, Vol 22Eb, Georg Thiem Verlag, New York (2002) pp. 715–738, (written and accepted in 2000).

- "Spectroscopic Studies of Structural Changes in Two beta-Sheet Forming Peptides Show an Ensemble of Structures That Unfold Non-Cooperatively" Serguei V. Kuznetsov, Jovencio Hilario, T. A. Keiderling, Anjum Ansari, *Biochemistry*, 42 :4321-4332, (2003).

- "Optical spectroscopic investigations of model beta-sheet hairpins in aqueous solution" Jovencio Hilario, Jan Kubelka, T. A. Keiderling, *Journal of the American Chemical Society* 125, 7562-7574 (2003).

- "Synthesis and conformational study of homopeptides based on (S)-Bin, a C2-symmetric binapthyl-derived Caa-disubstituted glycine with only axial chirality" J.-P. Mazaleyrat, K. Wright, A. Gaucher, M. Wakselman, S. Oancea, F. Formaggio, C. Toniolo, V. Setnicka, J. Kapitan, T. A. Keiderling, Tetrahedron Asymmetry, 14, 1879-1893 (2003).
- "Empirical modeling of the peptide amide I band IR intensity in water solution," Petr Bour, Timothy A. Keiderling, *Journal of Chemical Physics*, 119, 11253-11262 (2003)
- "The Nature of Vibrational Coupling in Helical Peptides: An Isotope Labeling Study" by R. Huang, J. Kubelka, W. Barber-Armstrong, R. A. G. D Silva, S. M. Decatur, and T. A. Keiderling, *Journal of the American Chemical Society*, 126, 2346-2354 (2004).
- "The Complete Chirospectroscopic Signature of the Peptide 3_{10} Helix in Aqueous Solution" Claudio Toniolo, Fernando Formaggio, Sabrina Tognon, Quirinus B. Broxterman, Bernard Kaptein, Rong Huang, Vladimir Setnicka, Timothy A. Keiderling, Iain H. McColl, Lutz Hecht, Laurence D. Barron, Biopolymers 75, 32-45 (2004).
- "Induced axial chirality in the biphenyl core for the Ca-tetrasubstituted a-amino acid residue Bip and subsequent propagation of chirality in (Bip)n/Val oligopeptides" J.-P. Mazaleyrat, K. Wright, A. Gaucher, N. Toulemonde, M. Wakselman, S. Oancea, C. Peggion, F. Formaggio, V. Setnicka, T. A. Keiderling, C. Toniolo, *Journal of the American Chemical Society* 126; 12874-12879 (2004).
- *Ab initio* modeling of amide I coupling in anti-parallel b-sheets and the effect of the 13C isotopic labeling on vibrational spectra" Petr Bour, Timothy A. Keiderling, *Journal of Physical Chemistry B*, 109, 5348-5357 (2005)
- Solvent Effects on IR And VCD Spectra of Helical Peptides: Insights from Ab Initio Spectral Simulations with Explicit Water" Jan Kubelka and Timothy A. Keiderling, Journal of Physical Chemistry B 109, 8231-8243 (2005)
- IR Study of Cross-Strand Coupling in a beta-Hairpin Peptide Using Isotopic Labels., Vladimir Setnicka, Rong Huang, Catherine L. Thomas, Marcus A. Etienne, Jan Kubelka, Robert P. Hammer, Timothy A. Keiderling *Journal of the American Chemical Society* 127, 4992-4993 (2005).
- Vibrational spectral simulation for peptides of mixed secondary structure: Method comparisons with the trpzip model hairpin. Petr Bour and Timothy A. Keiderling, *Journal of Physical Chemistry B* 109, 232687-23697 (2005).
- Isotopically labeled peptides provide site-resolved structural data with infrared spectra. Probing the structural limit of optical spectroscopy, Timothy A. Keiderling, Rong Huang, Jan Kubelka, Petr Bour, Vladimir Setnicka, Robert P. Hammer, Marcus *A. Etienne, R. A. Gangani D. Silva, Sean M. Decatur Collections Symposium Series, 8, 42-49 (2005)—["Biologically Active Peptides" IXth Conference, Prague Czech Republic, April 20-22, 2005.

Nucleic acids and polynucleotides

- "Application of Vibrational Circular Dichroism to Synthetic Polypeptides and Polynucleic Acids" T. A. Keiderling, S. C. Yasui, R. K. Dukor, L. Yang, Polymer Preprints 30, 423-424 (1989).
- "Vibrational Circular Dichroism of Polyribonucleic Acids. A Comparative Study in Aqueous Solution." A. Annamalai and T. A. Keiderling, *Journal of the American Chemical Society*, 109, 3125-3132 (1987).
- "Conformational phase transitions (A-B and B-Z) of DNA and models using vibrational circular dichroism" L. Wang, L. Yang, T. A. Keiderling in *Spectroscopy of Biological Molecules.*, eds. R. E. Hester, R. B. Girling, Special Publication 94 Roya l Society of Chemistry, Cambridge (1991) p. 137-38.
- "Vibrational Circular Dichroism of Proteins Polysaccharides and Nucleic Acids" T. A. Keiderling, Chapter 8 in *Physical Chemistry of Food Processes, Vol. 2 Advanced Techniques, Structures and Applications* eds. I. C. Baianu, H. Pessen, T. Kumosinski, Van Norstrand—Reinhold, New York (1993) pp. 307–337.
- "Structural Studies of Biological Macromolecules using Vibrational Circular Dichroism" T. A. Keiderling, P. Pancoska, Chapter 6 in Advances in Spectroscopy Vol. 21, "Biomolecular Spectroscopy Part B" ed. R. E. Hester, R. J. H. Clarke, John W iley Chichester (1993) pp 267–315.

- "Detection of Triple Helical Nucleic Acids with Vibrational Circular Dichroism," L. Wang, P. Pancoska, T. A. Keiderling in "Fifth International Conference on The Spectroscopy of Biological Molecules" Th. Theophanides, J. Anastassopoulou, N. Fotopoul os (Eds), Kluwen Academic Publ., Dortrecht, 1993, p. 81-82.
- "Helical Nature of Poly (dI-dC) � Poly (dI-dC). Vibrational Circular Dichroism Results" L. Wang and T. A. Keiderling Nucleic Acids Research 21 4127-4132 (1993).
- "Detection and Characterization of Triple Helical Pyrimidine-Purine-Pyrimidine Nucleic Acids with Vibrational Circular Dichroism" L. Wang, P. Pancoska, T. A. Keiderling, Biochemistry 33 8428-8435 (1994).
- "Vibrational Circular Dichroism of A-, B- and Z- form Nucleic Acids in the PO2- Stretching Region" L. Wang, L. Yang, T. A. Keiderling, Biophysical Journal 67, 2460-2467 (1994).
- "Studies of multiple stranded RNA and DNA with FTIR, vibrational and electronic circular dichroism," Zhihua Huang, Lijiang Wang and Timothy A. Keiderling, in Spectrosopy of Biological Molecules, Ed. J. C. Merlin, Kluwer Acad. Pub., Dordrecht, 1995, pp . 321-322.
- "Vibrational Circular Dichroism Applications to Conformational Analysis of Biomolecules" T. A. Keiderling in "Circular Dichroism and the Conformational Analysis of Biomolecules" ed G. D. Fasman, Plenum, New York (1996) pp. 555–598.
- "Vibrational Circular Dichroism Techniques and Application to Nucleic Acids" T. A. Keiderling, In "Biomolecular Structure and Dynamics", NATO ASI series, Series E: Applied Sciences- Vol.342, Eds: G. Vergoten and T. Theophanides, Kluwer Academ ic Publishers, Dordrecht, The Netherlands,pp. 299–317 (1997).

See also

- Circular dichroism
- Birefringence
- Optical rotatory dispersion
- IR spectroscopy
- Polarization
- Proteins
- Nucleic Acids
- DNA
- Molecular models of DNA
- DNA structure
- Protein structure
- Amino acids
- Density functional theory
- Quantum chemistry
- Raman optical activity (ROA)

References

[1] http://planetphysics.org/?op=getobj;from=objects;id=410 Principles of IR and NIR Spectroscopy

[2] *"Vibrational Circular Dichroism of Polypeptides XII. Re-evaluation of the Fourier Transform Vibrational Circular Dichroism of Poly-gamma-Benzyl-L-Glutamate," P. Malon, R. Kobrinskaya, T. A. Keiderling, Biopolymers 27, 733-746 (1988).

[3] *"Vibrational Circular Dichroism of Biopolymers," T. A. Keiderling, S. C. Yasui, U. Narayanan, A. Annamalai, P. Malon, R. Kobrinskaya, L. Yang, in *Spectroscopy of Biological Molecules New Advances* ed. E. D. Schmid, F. W. Schneider, F. Siebert, p. 73-76 (1988).

[4] *"Vibrational Circular Dichroism of Polypeptides and Proteins," S. C. Yasui, T. A. Keiderling, *Mikrochimica Acta*, II, 325-327, (1988).

[5] *"Vibrational Circular Dichroism of Proteins Polysaccharides and Nucleic Acids" T. A. Keiderling, Chapter 8 in *Physical Chemistry of Food Processes, Vol. 2 Advanced Techniques, Structures and Applications.*, eds. I.C. Baianu, H. Pessen, T. Kumosinski, Van Norstrand--Reinhold, New York (1993), pp 307-337.

[6] "Spectroscopic characterization of Unfolded peptides and proteins studied with infrared absorption and vibrational circular dichroism spectra" T. A. Keiderling and Qi Xu, Advances in Protein Chemistry Volume 62, [Unfolded Proteins, Dedicated to John Edsall, Ed.: George Rose, Academic Press:New York] (2002), pp. 111-161.

[7] *"Protein and Peptide Secondary Structure and Conformational Determination with Vibrational Circular Dichroism " Timothy A. Keiderling, *Current Opinions in Chemical Biology* (Ed. Julie Leary and Mark Arnold) 6, 682-688 (2002).

[8] *Review: Conformational Studies of Peptides with Infrared Techniques. Timothy A. Keiderling and R. A. G. D. Silva, in Synthesis of Peptides and Peptidomimetics, Ed. M. Goodman and G. Herrman, Houben-Weyl, Vol 22Eb, Georg Thiem Verlag, New York (2002) pp. 715-738, (written and accepted in 2000).

[9] "Polarization Modulation Fourier Transform Infrared Spectroscopy with Digital SignalProcessing: Comparison of Vibrational Circular Dichroism Methods." Jovencio Hilario, DavidDrapcho, Raul Curbelo, Timothy A. Keiderling, Applied Spectroscopy 55, 1435-1447(2001)--

[10] "Vibrational circular dichroism of biopolymers. Summary of methods and applications.", Timothy A. Keiderling, Jan Kubelka, Jovencio Hilario, in *Vibrational spectroscopy of polymers and biological systems*, Ed. Mark Braiman, Vasilis Gregoriou, Taylor&Francis, Atlanta (CRC Press, Boca Raton, FL) (2006) pp. 253-324 (originally written in 2000, updated in 2003)

[11] "Observation of Magnetic Vibrational Circular Dichroism," T. A. Keiderling, Journal of Chemical Physics, 75, 3639-41 (1981).

[12] "Vibrational Spectral Assignment and Enhanced Resolution Using Magnetic Vibrational Circular Dichroism," T. R. Devine and T. A. Keiderling, *Spectrochimica Acta*, 43A, 627-629 (1987).

[13] "Magnetic Vibrational Circular Dichroism with an FTIR" P. V. Croatto, R. K. Yoo, T. A. Keiderling, SPIE Proceedings 1145 (7th International Conference on FTS, ed. D. G. Cameron) 152-153 (1989).

[14] "Direct Measurement of the Rotational g-Value in the Ground State of Acetylene by Magnetic Vibrational Circular Dichroism." C. N. Tam and T. A. Keiderling, Chemical Physics Letters, 243, 55-58 (1995).

[15] . "Ab initio calculation of the vibrational magnetic dipole moment" P. Bour, C. N. Tam, T. A. Keiderling, Journal of Physical Chemistry 99, 17810-17813 (1995)

[16] "Rotationally Resolved Magnetic Vibrational Circular Dichroism. Experimental Spectra and Theoretical Simulation for Diamagnetic Molecules." P. Bour, C. N. Tam, B. Wang, T. A. Keiderling, *Molecular Physics* 87, 299-318, (1996).

Chemical imaging

Chemical imaging is the analytical capability (as quantitative - mapping) to create a visual image from simultaneous measurement of spectra (as quantitative - chemical) and spatial, time informations. [1] [2] The technique is most often applied to either solid or gel samples, and has applications in chemistry, biology[3] [4] [5] [6] [7] [8] , medicine[9] [10] , pharmacy[11] (see also for example: Chemical Imaging Without Dyeing [12]), food science, biotechnology[13] [14] , agriculture and industry (see for example:NIR Chemical Imaging in Pharmaceutical Industry [15] and Pharmaceutical Process Analytical Technology: [16]). NIR, IR and Raman chemical imaging is also referred to as hyperspectral, spectroscopic, spectral or multispectral imaging (also see microspectroscopy). However, other ultra-sensitive and selective, chemical imaging techniques are also in use that involve either UV-visible or fluorescence microspectroscopy. Chemical imaging techniques can be used to analyze samples of all sizes, from the single molecule[17] [18] to the cellular level in biology and medicine[19] [20] [21] , and to images of planetary systems in astronomy, but different instrumentation is employed for making observations on such widely different systems.

Chemical imaging instrumentation is composed of three components: a radiation source to illuminate the sample, a spectrally selective element, and usually a detector array (the camera) to collect the images. When many stacked spectral channels (wavelengths) are collected for different locations of the microspectrometer focus on a line or planar array in the focal plane, the data is called hyperspectral; fewer wavelength data sets are called multispectral. The data format is called a hypercube. The data set may be visualized as a three-dimensional block of data spanning two spatial dimensions (x and y), with a series of wavelengths (lambda) making up the third (spectral) axis. The hypercube can be visually and mathematically treated as a series of spectrally resolved images (each image plane corresponding to the image at one wavelength) or a series of spatially resolved spectra. The analyst may choose to view the spectrum measured at a particular spatial location; this is useful for chemical identification. Alternatively, selecting an image plane at a particular wavelength can highlight the spatial distribution of sample components, provided that their spectral signatures are different at the selected wavelength.

Many materials, both manufactured and naturally occurring, derive their functionality from the spatial distribution of sample components. For example, extended release pharmaceutical formulations can be achieved by using a coating that acts as a barrier layer. The release of active ingredient is controlled by the presence of this barrier, and imperfections in the coating, such as discontinuities, may result in altered performance. In the semi-conductor industry, irregularities or contaminants in silicon wafers or printed micro-circuits can lead to failure of these components. The functionality of biological systems is also dependent upon chemical gradients − a single cell, tissue, and even whole organs function because of the very specific arrangement of components. It has been shown that even small changes in chemical composition and distribution may be an early indicator of disease.

Any material that depends on chemical gradients for functionality may be amenable to study by an analytical technique that couples spatial and chemical characterization. To efficiently and effectively design and manufacture such materials, the 'what' and the 'where' must both be measured. The demand for this type of analysis is increasing as manufactured materials become more complex. Chemical imaging techniques not only permit visualization of the spatially resolved chemical information that is critical to understanding modern manufactured products, but it is also a non-destructive technique so that samples are preserved for further testing.

History

Commercially available laboratory-based chemical imaging systems emerged in the early 1990s (ref. 1-5). In addition to economic factors, such as the need for sophisticated electronics and extremely high-end computers, a significant barrier to commercialization of infrared imaging was that the focal plane array (FPA) needed to read IR images were not readily available as commercial items. As high-speed electronics and sophisticated computers became more commonplace, and infrared cameras became readily commercially available, laboratory chemical imaging systems were introduced.

Initially used for novel research in specialized laboratories, chemical imaging became a more commonplace analytical technique used for general R&D, quality assurance (QA) and quality control (QC) in less than a decade. The rapid acceptance of the technology in a variety of industries (pharmaceutical, polymers, semiconductors, security, forensics and agriculture) rests in the wealth of information characterizing both chemical composition and morphology. The parallel nature of chemical imaging data makes it possible to analyze multiple samples simultaneously for applications that require high throughput analysis in addition to characterizing a single sample.

Principles

Chemical imaging shares the fundamentals of vibrational spectroscopic techniques, but provides additional information by way of the simultaneous acquisition of spatially resolved spectra. It combines the advantages of digital imaging with the attributes of spectroscopic measurements. Briefly, vibrational spectroscopy measures the interaction of light with matter. Photons that interact with a sample are either absorbed or scattered; photons of specific energy are absorbed, and the pattern of absorption provides information, or a fingerprint, on the molecules that are present in the sample.

On the other hand, in terms of the observation setup, chemical imaging can be carried out in one of the following modes: (optical) absorption, emission (fluorescence), (optical) transmission or scattering (Raman). A consensus currently exists that the fluorescence (emission) and Raman scattering modes are the most sensitive and powerful, but also the most expensive.

In a transmission measurement, the radiation goes through a sample and is measured by a detector placed on the far side of the sample. The energy transferred from the incoming radiation to the molecule(s) can be calculated as the difference between the quantity of photons that were emitted by the source and the quantity that is measured by the detector. In a diffuse reflectance measurement, the same energy difference measurement is made, but the source and detector are located on the same side of the sample, and the photons that are measured have re-emerged from the illuminated side of the sample rather than passed through it. The energy may be measured at one or multiple wavelengths; when a series of measurements are made, the response curve is called a spectrum.

A key element in acquiring spectra is that the radiation must somehow be energy selected − either before or after interacting with the sample. Wavelength selection can be accomplished with a fixed filter, tunable filter, spectrograph, an interferometer, or other devices. For a fixed filter approach, it is not efficient to collect a significant number of wavelengths, and multispectral data are usually collected. Interferometer-based chemical imaging requires that entire spectral ranges be collected, and therefore results in hyperspectral data. Tunable filters have the flexibility to provide either multi- or hyperspectral data, depending on analytical requirements.

Spectra may be measured one point at a time using a single element detector (single-point mapping), as a line-image using a linear array detector (typically 16 to 28 pixels) (linear array mapping), or as a two-dimensional image using a Focal Plane Array (FPA)(typically 256 to 16,384 pixels) (FPA imaging). For single-point the sample is moved in the x and y directions point-by-point using a computer-controlled stage. With linear array mapping, the sample is moved line-by-line with a computer-controlled stage. FPA imaging data are collected with a two-dimensional FPA detector, hence capturing the full desired field-of-view at one time for each individual wavelength, without having to move the sample. FPA imaging, with its ability to collected tens of thousands of spectra simultaneously is orders of magnitude faster than linear arrays which are can typically collect 16 to 28 spectra simultaneously, which are in turn much faster than single-point mapping.

Terminology

Some words common in spectroscopy, optical microscopy and photography have been adapted or their scope modified for their use in chemical imaging. They include: resolution, field of view and magnification. There are two types of resolution in chemical imaging. The spectral resolution refers to the ability to resolve small energy differences; it applies to the spectral axis. The spatial resolution is the minimum distance between two objects that is required for them to be detected as distinct objects. The spatial resolution is influenced by the field of view, a physical measure of the size of the area probed by the analysis. In imaging, the field of view is a product of the magnification and the number of pixels in the detector array. The magnification is a ratio of the physical area of the detector array divided by the area of the sample field of view. Higher magnifications for the same detector image a smaller area of the sample.

Types of vibrational chemical imaging instruments

Chemical imaging has been implemented for mid-infrared, near-infrared spectroscopy and Raman spectroscopy. As with their bulk spectroscopy counterparts, each imaging technique has particular strengths and weaknesses, and are best suited to fulfill different needs.

Mid-infrared chemical imaging

Mid-infrared (MIR) spectroscopy probes fundamental molecular vibrations, which arise in the spectral range 2,500-25,000 nm. Commercial imaging implementations in the MIR region typically employ Fourier Transform Infrared (FT-IR) interferometers and the range is more commonly presented in wavenumber, $4,000 - 400 \text{ cm}^{-1}$. The MIR absorption bands tend to be relatively narrow and well-resolved; direct spectral interpretation is often possible by an experienced spectroscopist. MIR spectroscopy can distinguish subtle changes in chemistry and structure, and is often used for the identification of unknown materials. The absorptions in this spectral range are relatively strong; for this reason, sample presentation is important to limit the amount of material interacting with the incoming radiation in the MIR region. Most data collected in this range is collected in transmission mode through thin sections (~10 micrometres) of material. Water is a very strong absorber of MIR radiation and wet samples often require advanced sampling procedures (such as attenuated total reflectance). Commercial instruments include point and line mapping, and imaging. All employ an FT-IR interferometer as wavelength selective element and light source.

For types of MIR microscope, see Microscopy#infrared microscopy.

Atmospheric windows in the infrared spectrum are also employed to perform chemical imaging remotely. In these spectral regions the atmospheric gases (mainly water and CO_2) present low absorption and allow infrared viewing over kilometer distances. Target molecules can then be viewed using the selective absorption/emission processes

Remote chemical imaging of a simultaneous release of SF_6 and NH_3 at 1.5km using the FIRST imaging spectrometer[22]

described above. An example of the chemical imaging of a simultaneous release of SF_6 and NH_3 is shown in the image.

Near-infrared chemical imaging

The analytical near infrared (NIR) region spans the range from approximately 700-2,500 nm. The absorption bands seen in this spectral range arise from overtones and combination bands of O-H, N-H, C-H and S-H stretching and bending vibrations. Absorption is one to two orders of magnitude smaller in the NIR compared to the MIR; this phenomenon eliminates the need for extensive sample preparation. Thick and thin samples can be analyzed without any sample preparation, it is possible to acquire NIR chemical images through some packaging materials, and the technique can be used to examine hydrated samples, within limits. Intact samples can be imaged in transmittance or diffuse reflectance.

The lineshapes for overtone and combination bands tend to be much broader and more overlapped than for the fundamental bands seen in the MIR. Often, multivariate methods are used to separate spectral signatures of sample components. NIR chemical imaging is particularly useful for performing rapid, reproducible and non-destructive analyses of known materials[23] [24] . NIR imaging instruments are typically based on one of two platforms: imaging using a tunable filter and broad band illumination, and line mapping employing an FT-IR interferometer as the wavelength filter and light source.

Raman chemical imaging

The Raman shift chemical imaging spectral range spans from approximately 50 to 4,000 cm^{-1}; the actual spectral range over which a particular Raman measurement is made is a function of the laser excitation frequency. The basic principle behind Raman spectroscopy differs from the MIR and NIR in that the x-axis of the Raman spectrum is measured as a function of energy shift (in cm^{-1}) relative to the frequency of the laser used as the source of radiation. Briefly, the Raman spectrum arises from inelastic scattering of incident photons, which requires a change in polarizability with vibration, as opposed to infrared absorption, which requires a change in dipole moment with vibration. The end result is spectral information that is similar and in many cases complementary to the MIR. The Raman effect is weak - only about one in 10^7 photons incident to the sample undergoes Raman scattering. Both organic and inorganic materials possess a Raman spectrum; they generally produce sharp bands that are chemically specific. Fluorescence is a competing phenomenon and, depending on the sample, can overwhelm the Raman signal, for both bulk spectroscopy and imaging implementations.

Raman chemical imaging requires little or no sample preparation. However, physical sample sectioning may be used to expose the surface of interest, with care taken to obtain a surface that is as flat as possible. The conditions required for a particular measurement dictate the level of invasiveness of the technique, and samples that are sensitive to high power laser radiation may be damaged during analysis. It is relatively insensitive to the presence of water in the sample and is therefore useful for imaging samples that contain water such as biological material.

Fluorescence imaging (visible and NIR)

This emission microspectroscopy mode is the most sensitive in both visible and FT-NIR microspectroscopy, and has therefore numerous biomedical, biotechnological and agricultural applications. There are several powerful, highly specific and sensitive fluorescence techniques that are currently in use, or still being developed; among the former are FLIM, FRAP, FRET and FLIM-FRET; among the latter are NIR fluorescence and probe-sensitivity enhanced NIR fluorescence microspectroscopy and nanospectroscopy techniques (see "Further reading" section).

Sampling and samples

The value of imaging lies in the ability to resolve spatial heterogeneities in solid-state or gel/gel-like samples. Imaging a liquid or even a suspension has limited use as constant sample motion serves to average spatial information, unless ultra-fast recording techniques are employed as in fluorescence correlation microspectroscopy or FLIM obseVations where a single molecule may be monitored at extremely high (photon) detection speed. High-throughput experiments (such as imaging multi-well plates) of liquid samples can however provide valuable

information. In this case, the parallel acquisition of thousands of spectra can be used to compare differences between samples, rather than the more common implementation of exploring spatial heterogeneity within a single sample.

Similarly, there is no benefit in imaging a truly homogeneous sample, as a single point spectrometer will generate the same spectral information. Of course the definition of homogeneity is dependent on the spatial resolution of the imaging system employed. For MIR imaging, where wavelengths span from 3-10 micrometres, objects on the order of 5 micrometres may theoretically be resolved. The sampled areas are limited by current experimental implementations because illumination is provided by the interferometer. Raman imaging may be able to resolve particles less than 1 micrometre in size, but the sample area that can be illuminated is severely limited. With Raman imaging, it is considered impractical to image large areas and, consequently, large samples. FT-NIR chemical/hyperspectral imaging usually resolves only larger objects (>10 micrometres), and is better suited for large samples because illumination sources are readily available. However, FT-NIR microspectroscopy was recently reported to be capable of about 1.2 micron (micrometer) resolution in biological samples[25] Furthermore, two-photon excitation FCS experiments were reported to have attained 15 nanometer resolution on biomembrane thin films with a special coincidence photon-counting setup.

Detection limit

The concept of the detection limit for chemical imaging is quite different than for bulk spectroscopy, as it depends on the sample itself. Because a bulk spectrum represents an average of the materials present, the spectral signatures of trace components are simply overwhelmed by dilution. In imaging however, each pixel has a corresponding spectrum. If the physical size of the trace contaminant is on the order of the pixel size imaged on the sample, its spectral signature will likely be detectable. If however, the trace component is dispersed homogeneously (relative to pixel image size) throughout a sample, it will not be detectable. Therefore, detection limits of chemical imaging techniques are strongly influenced by particle size, the chemical and spatial heterogeneity of the sample, and the spatial resolution of the image.

Data analysis

Data analysis methods for chemical imaging data sets typically employ mathematical algorithms common to single point spectroscopy or to image analysis. The reasoning is that the spectrum acquired by each detector is equivalent to a single point spectrum; therefore pre-processing, chemometrics and pattern recognition techniques are utilized with the similar goal to separate chemical and physical effects and perform a qualitative or quantitative characterization of individual sample components. In the spatial dimension, each chemical image is equivalent to a digital image and standard image analysis and robust statistical analysis can be used for feature extraction.

See also

- chemical mapping
- Multispectral image
- Microspectroscopy
- Imaging spectroscopy

Further reading

1. E. N. Lewis, P. J. Treado, I. W. Levin, Near-Infrared and Raman Spectroscopic Imaging, American Laboratory, 06/1994:16 (1994)
2. E. N. Lewis, P. J. Treado, R. C. Reeder, G. M. Story, A. E. Dowrey, C. Marcott, I. W. Levin, FTIR spectroscopic imaging using an infrared focal-plane array detector, Analytical Chemistry, 67:3377 (1995)

3. P. Colarusso, L. H. Kidder, I. W. Levin, J. C. Fraser, E. N. Lewis Infrared Spectroscopic Imaging: from Planetary to Cellular Systems, Applied Spectroscopy, 52 (3):106A (1998)

4. P. J. Treado I. W. Levin, E. N. Lewis, Near-Infrared Spectroscopic Imaging Microscopy of Biological Materials Using an Infrared Focal-Plane Array and an Acousto-Optic Tunable Filter (AOTF), Applied Spectroscopy, 48:5 (1994)

5. Hammond, S.V., Clarke, F. C., Near-infrared microspectroscopy. In: Handbook of Vibrational Spectroscopy, Vol. 2, J.M. Chalmers and P.R. Griffiths Eds. John Wiley and Sons, West Sussex, UK, 2002, p.1405-1418

6. L.H. Kidder, A.S. Haka, E.N. Lewis, Instrumentation for FT-IR Imaging. In: Handbook of Vibrational Spectroscopy, Vol. 2, J.M. Chalmers and P.R. Griffiths Eds. John Wiley and Sons, West Sussex, UK, 2002, pp.1386-1404

7. J. Zhang; A. O'Connor; J. F. Turner II, Cosine Histogram Analysis for Spectral Image Data Classification,Applied Spectroscopy, Volume 58, Number 11, November 2004, pp. 1318-1324(7)

8. J. F. Turner II; J. Zhang; A. O'Connor, A Spectral Identity Mapper for Chemical Image Analysis, Applied Spectroscopy, Volume 58, Number 11, November 2004, pp. 1308-1317(10)

9. H. R. MORRIS, J. F. TURNER II, B. MUNRO, R. A. RYNTZ, P. J. TREADO, Chemical imaging of thermoplastic olefin (TPO) surface architecture, Langmuir, 1999, vol. 15, no8, pp. 2961-2972

10. J. F. Turner II, Chemical imaging and spectroscopy using tunable filters: Instrumentation, methodology, and multivariate analysis, Thesis (PhD). UNIVERSITY OF PITTSBURGH, Source DAI-B 59/09, p. 4782, Mar 1999, 286 pages.

11. P. Schwille.(2001). in *Fluorescence Correlation Spectroscopy. Theory and applications.* R. Rigler & E.S. Elson, eds., p. 360. Springer Verlag: Berlin.

12. Schwille P., Oehlenschläger F. and Walter N. (1996). Analysis of RNA-DNA hybridization kinetics by fluorescence correlation spectroscopy, *Biochemistry* **35**:10182.

13. FLIM | Fluorescence Lifetime Imaging Microscopy: Fluorescence, fluorophore chemical imaging, confocal emission microspectroscopy, FRET, cross-correlation fluorescence microspectroscopy [26].

14. FLIM Applications: [26] "FLIM is able to discriminate between fluorescence emanating from different fluorophores and autoflorescing molecules in a specimen, even if their emission spectra are similar. It is, therefore, ideal for identifying fluorophores in multi-label studies. FLIM can also be used to measure intracellular ion concentrations without extensive calibration procedures (for example, Calcium Green) and to obtain information about the local environment of a fluorophore based on changes in its lifetime." FLIM is also often used in microspectroscopic/chemical imaging, or microscopic, studies to monitor spatial and temporal protein-protein interactions, properties of membranes and interactions with nucleic acids in living cells.

15. Gadella TW Jr., *FRET and FLIM techniques*, 33. Imprint: Elsevier, ISBN 978-0-08-054958-3. (2008) 560 pages

16. Langel FD, et al., Multiple protein domains mediate interaction between Bcl10 and Malt1, *J. Biol. Chem.*, (2008) 283(47):32419-31

17. Clayton AH. , The polarized AB plot for the frequency-domain analysis and representation of fluorophore rotation and resonance energy homotransfer. J *Microscopy*. (2008) 232(2):306-12

18. Clayton AH, et al., Predominance of activated EGFR higher-order oligomers on the cell surface. *Growth Factors* (2008) 20:1

19. Plowman et al., Electrostatic Interactions Positively Regulate K-Ras Nanocluster Formation and Function. *Molecular and Cellular Biology* (2008) 4377–4385

20. Belanis L, et al., Galectin-1 Is a Novel Structural Component and a Major Regulator of H-Ras Nanoclusters. *Molecular Biology of the Cell* (2008) 19:1404–1414

21. Van Manen HJ, Refractive index sensing of green fluorescent proteins in living cells using fluorescence lifetime imaging microscopy. Biophys J. (2008) 94(8):L67-9

22. Van der Krogt GNM, et al., A Comparison of Donor-Acceptor Pairs for Genetically Encoded FRET Sensors: Application to the Epac cAMP Sensor as an Example, PLoS ONE, (2008) 3(4):e1916

23. Dai X, et al., Fluorescence intensity and lifetime imaging of free and micellar-encapsulated doxorubicin in living cells. *Nanomedicine*. (2008) **4**(1):49-56.

External links

- NIR Chemical Imaging in Pharmaceutical Industry [15]
- Pharmaceutical Process Analytical Technology: [16]
- NIR Chemical Imaging for Counterfeit Pharmaceutical Product Analysis [27]
- Chemical Imaging: Potential New Crime Busting Tool [28]

References

[1] http://www.imaging.net/chemical-imaging/Chemical imaging

[2] http://www.malvern.com/LabEng/products/sdi/bibliography/sdi_bibliography.htm E. N. Lewis, E. Lee and L. H. Kidder, Combining Imaging and Spectroscopy: Solving Problems with Near-Infrared Chemical Imaging. Microscopy Today, Volume 12, No. 6, 11/2004.

[3] C.L. Evans and X.S. Xie.2008. Coherent Anti-Stokes Raman Scattering Microscopy: Chemical Imaging for Biology and Medicine., doi:10.1146/annurev.anchem.1.031207.112754 *Annual Review of Analytical Chemistry*, **1**: 883-909.

[4] Diaspro, A., and Robello, M. (1999). Multi-photon Excitation Microscopy to Study Biosystems. European Microscopy and Analysis., 5:5-7.

[5] D.S. Mantus and G. H. Morrison. 1991. Chemical imaging in biology and medicine using ion microscopy., *Microchimica Acta*, **104**, (1-6) January 1991, doi: 10.1007/BF01245536

[6] Bagatolli, L.A., and Gratton, E. (2000). Two-photon fluorescence microscopy of coexisting lipid domains in giant unilamellar vesicles of binary phospholipid mixtures. Biophys J., 78:290-305.

[7] Schwille, P., Haupts, U., Maiti, S., and Webb. W.(1999). Molecular dynamics in living cells observed by fluorescence correlation spectroscopy with one- and two-photon excitation. Biophysical Journal, 77(10):2251-2265.

[8] 1.Lee, S. C. et al., (2001). One Micrometer Resolution NMR Microscopy. J. Magn. Res., 150: 207-213.

[9] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.

[10] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann and S. S. Korban, q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)

[11] J. Dubois, G. Sando, E. N. Lewis, Near-Infrared Chemical Imaging, A Valuable Tool for the Pharmaceutical Industry, G.I.T. Laboratory Journal Europe, No. 1-2, 2007.

[12] http://witec.de/en/download/Raman/ImagingMicroscopy04.pdf

[13] Raghavachari, R., Editor. 2001. *Near-Infrared Applications in Biotechnology*, Marcel-Dekker, New York, NY.

[14] Applications of Novel Techniques to Health Foods, Medical and Agricultural Biotechnology.(June 2004) I. C. Baianu, P. R. Lozano, V. I. Prisecaru and H. C. Lin q-bio/0406047 (http://arxiv.org/abs/q-bio/0406047)

[15] http://www.spectroscopyeurope.com/NIR_14_3.pdf

[16] http://www.fda.gov/cder/OPS/PAT.htm

[17] Eigen, M., and Rigler, R. (1994). Sorting single molecules: Applications to diagnostics and evolutionary biotechnology, Proc. Natl. Acad. Sci. USA 91:5740.

[18] Rigler R. and Widengren J. (1990). Ultrasensitive detection of single molecules by fluorescence correlation spectroscopy, *BioScience* (Ed. Klinge & Owman) p.180.

[19] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann, S. S. Korban and et al., q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)

[20] Oehlenschläger F., Schwille P. and Eigen M. (1996). Detection of HIV-1 RNA by nucleic acid sequence-based amplification combined with fluorescence correlation spectroscopy, *Proc. Natl. Acad. Sci. USA* **93**:1281.

[21] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.

[22] M. Chamberland, V. Farley, A. Vallières, L. Belhumeur, A. Villemaire, J. Giroux et J. Legault, High-Performance Field-Portable Imaging Radiometric Spectrometer Technology For Hyperspectral imaging Applications, Proc. SPIE 5994, 59940N, September 2005.

[23] Novel Techniques for Microspectroscopy and Chemical Imaging Analysis of Soybean Seeds and Embryos.(2002). Baianu, I.C., Costescu, D.M., and You, T. *Soy2002 Conference*, Urbana, Illinois.

[24] Near Infrared Microspectroscopy, Chemical Imaging and NMR Analysis of Oil in Developing and Mutagenized Soybean Embryos in Culture. (2003). Baianu, I.C., Costescu, D.M., Hofmann, N., and Korban, S.S. *AOCS Meeting, Analytical Division*.

[25] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D.

Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.

[26] http://www.nikoninstruments.com/infocenter.php?n=FLIM

[27] http://www.spectroscopymag.com/spectroscopy/Near-IR+Spectroscopy/NIR-Chemical-Imaging-for-Counterfeit-Pharmaceutica/ ArticleStandard/Article/detail/406629

[28] http://www.sciencedaily.com/releases/2007/08/070802103435.htm

Hyperspectral imaging

Hyperspectral imaging collects and processes information from across the electromagnetic spectrum. Unlike the human eye, which just sees visible light, hyperspectral imaging is more like the eyes of the mantis shrimp, which can see visible light as well as from the ultraviolet to infrared. Hyperspectral capabilities enable the mantis shrimp to recognize different types of coral, prey, or predators, all which may appear as the same color to the human eye.

Humans build sensors and processing systems to provide the same type of capability for application in agriculture, mineralogy, physics, and surveillance. Hyperspectral sensors look at objects using a vast portion of the electromagnetic spectrum. Certain objects leave unique 'fingerprints' across the electromagnetic spectrum. These 'fingerprints' are known as spectral signatures and enable identification of the materials that make up a scanned object. For example, having the spectral signature for oil helps mineralogists find new oil fields.

Acquisition and Analysis
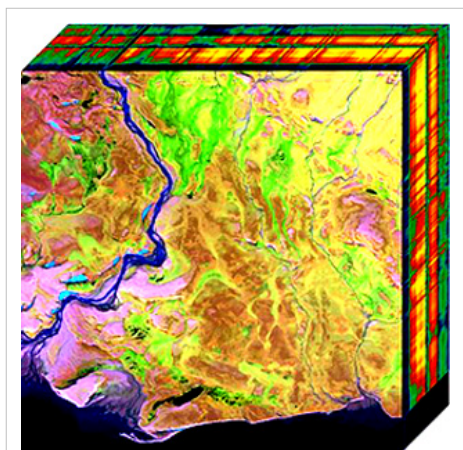
Example of a hyperspectral cube

Hyperspectral sensors collect information as a set of 'images'. Each image represents a range of the electromagnetic spectrum and is also known as a spectral band. These 'images' are then combined and form a three dimensional hyperspectral cube for processing and analysis.

Hyperspectral cubes are generated from airborne sensors like the NASA's *Airborne Visible/Infrared Imaging Spectrometer* (AVIRIS), or from satellites like NASA's Hyperion.[1] However, for many development and validation studies handheld sensors are used.[2]

The precision of these sensors is typically measured in spectral resolution, which is the width of each band of the spectrum that is captured. If the scanner picks up on a large number of fairly narrow frequency bands, it is possible to identify objects even if said objects are only captured in a handful of pixels. However, spatial resolution is a factor in addition to spectral resolution. If the pixels are too large, then multiple objects are captured in the same pixel and become difficult to identify. If the pixels are too small, then the energy captured by each sensor-cell is low, and the decreased signal-to-noise ratio reduces the reliability of measured features.

MicroMSI, Opticks and Envi are three remote sensing applications that support the processing and analysis of hyperspectral data. The acquisition and processing of hyperspectral images is also referred to as imaging spectroscopy.

Differences between hyperspectral and multispectral imaging

Hyperspectral imaging is part of a class of techniques commonly referred to as spectral imaging or spectral analysis. Hyperspectral imaging is related to multispectral imaging. The distinction between hyperspectral and multispectral is usually defined as the number of spectral bands. Multispectral data contains from tens to hundreds of bands. Hyperspectral data contains hundreds to thousands of bands. However, hyperspectral imaging may be best defined by the manner in which the data is collected. Hyperspectral data is a set of contiguous bands (usually by one sensor). Multispectral is a set of optimally chosen spectral bands that are typically not contiguous and can be collected from multiple sensors.

Hyperspectral and Multispectral Differences.
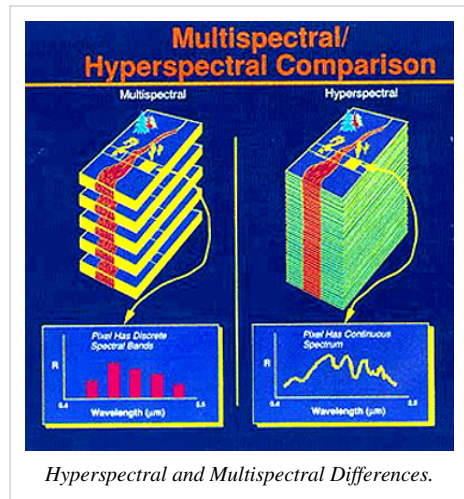
Applications

Hyperspectral remote sensing is used in a wide array of real-life applications. Although originally developed for mining and geology (the ability of hyperspectral imaging to identify various minerals makes it ideal for the mining and oil industries, where it can be used to look for ore and oil[2] [3]) it has now spread into fields as widespread as ecology and surveillance, as well as historical manuscript research such as the imaging of the Archimedes Palimpsest. This technology is continually becoming more available to the public, and has been used in a wide variety of ways. Organizations such as NASA and the USGS have catalogues of various minerals and their spectral signatures, and have posted them online to make them readily available for researchers.

Agriculture

Although the costs of acquiring hyperspectral images is typically high, for specific crops and in specific climates hyperspectral remote sensing is used more and more for monitoring the development and health of crops. In Australia work is underway to use imaging spectrometers to detect grape variety, and develop an early warning system for disease outbreaks.[4] Furthermore work is underway to use hyperspectral data to detect the chemical composition of plants[5] which can be used to detect the nutrient and water status of wheat in irrigated systems[6]

Mineralogy

The original field of development for hyperspectral remote sensing, hyperspectral sensing of minerals is now well developed. Many minerals can be identified from images, and their relation to the presence of valuable minerals such as gold and diamonds is well understood. Currently the move is towards understanding the relation between oil and gas leakages from pipelines and natural wells; their effect on the vegetation and the spectral signatures. Recent work includes the PhD dissertations of Werff[7] and Noomen[8] .

Physics

Physicists use an electron microscopy technique that involves microanalysis using either Energy dispersive X-ray spectroscopy (EDS), Electron energy loss spectroscopy (EELS), Infrared Spectroscopy(IR), Raman Spectroscopy, or cathodoluminescence (CL) spectroscopy, in which the entire spectrum measured at each point is recorded. EELS hyperspectral imaging is performed in a scanning transmission electron microscope (STEM); EDS and CL mapping can be performed in STEM as well, or in a scanning electron microscope or electron probe microanalyzer (EPMA).

Often, multiple techniques (EDS, EELS, CL) are used simultaneously.

In a "normal" mapping experiment, an image of the sample will be made that is simply the intensity of a particular emission mapped in an XY raster. For example, an EDS map could be made of a steel sample, in which iron x-ray intensity is used for the intensity grayscale of the image. Dark areas in the image would indicate not-iron-bearing impurities. This could potentially give misleading results; if the steel contained tungsten inclusions, for example, the high atomic number of tungsten could result in bremsstrahlung radiation that made the iron-free areas *appear* to be rich in iron.

By hyperspectral mapping, instead, the entire spectrum at each mapping point is acquired, and a quantitative analysis can be performed by computer post-processing of the data, and a quantitative map of iron content produced. This would show which areas contained no iron, despite the anomalous x-ray counts caused by bremsstrahlung. Because EELS core-loss edges are small signals on top of a large background, hyperspectral imaging allows large improvements to the quality of EELS chemical maps.

Similarly, in CL mapping, small shifts in the peak emission energy could be mapped, which would give information regarding slight chemical composition changes or changes in the stress state of a sample.

Surveillance

Hyperspectral surveillance is the implementation of hyperspectral scanning technology for surveillance purposes. Hyperspectral imaging is particularly useful in military surveillance because of measures that military entities now take to avoid airborne surveillance. Airborne surveillance has been in effect since soldiers used tethered balloons to spy on troops during the American Civil War, and since that time we have learned not only to hide from the naked eye, but to mask our heat signature to blend in to the surroundings and avoid infrared scanning, as well. The idea that drives hyperspectral surveillance is that hyperspectral scanning draws information from such a large portion of the light spectrum that any given object should have unique spectral signature in at least a few of the many bands that get scanned.[1]

Advantages and disadvantages

The primary advantages to hyperspectral imaging is that, because an entire spectrum is acquired at each point, the operator needs no prior knowledge of the sample, and post-processing allows all available information from the dataset to be mined.

The primary disadvantages are cost and complexity. Fast computers, sensitive detectors, and large data storage capacities are needed for analyzing hyperspectral data. Significant data storage capacity is necessary since hyperspectral cubes are large multi-dimensional datasets, potentially exceeding hundreds of megabytes. All of these factors greatly increase the cost of acquiring and processing hyperspectral data. Also, one of the hurdles that researchers have had to face is finding ways to program hyperspectral satellites to sort through data on their own and transmit only the most important images, as both transmission and storage of that much data could prove difficult and costly.[1] As a relatively new analytical technique, the full potential of hyperspectral imaging has not yet been realized.

See also

- Airborne Real-time Cueing Hyperspectral Enhanced Reconnaissance
- Full Spectral Imaging
- Multi-spectral image
- Chemical imaging
- Remote Sensing
- Sensor fusion
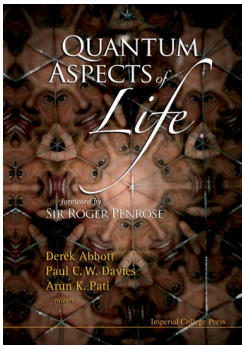
External links

- ITT Visual Information Solutions - ENVI Hyperspectral Image Processing Software [9]
- A Hyperspectral Imaging Prototype [10] Fourier transform spectroscopy is combined with Fabry-Perot interferometry
- Middleton Research [11] Hyperspectral Imaging products, custom engineering solutions
- Photon etc. [12] Hyperspectral Imaging Systems
- UmBio - Evince. Hyperspectral image analysis in real-time. Visual information solutions, see industrial demo movies [13]
- A Matlab Hyperspectral Toolbox [14]
- Telops Hyper-Cam [15] Commercial infrared hyperspectral camera

References

[1] Schurmer, J.H., (Dec 2003), Air Force Research Laboratories Technology Horizons

[2] Ellis, J., (Jan 2001) *Searching for oil seeps and oil-impacted soil with hyperspectral imagery* (http://www.eomonline.com/Common/currentissues/Jan01/ellis.htm)*, Earth Observation Magazine.

[3] Smith, R.B. (July 14, 2006), *Introduction to hyperspectral imaging with TMIPS* (http://www.microimages.com/getstart/pdf/hyprspec.pdf), MicroImages Tutorial Web site

[4] Lacar, F.M., et al., *Use of hyperspectral imagery for mapping grape varieties in the Barossa Valley, South Australia* (http://hdl.handle.net/2440/39292), Geoscience and remote sensing symposium (IGARSS'01) - IEEE 2001 International, vol.6 2875-2877p. doi: 10.1109/IGARSS.2001.978191 (http://dx.doi.org/10.1109/IGARSS.2001.978191)

[5] Ferwerda, J.G. (2005), *Charting the quality of forage: measuring and mapping the variation of chemical components in foliage with hyperspectral remote sensing* (http://www.itc.nl/library/Papers_2005/phd/ferwerda.pdf), Wageningen University , ITC Dissertation 126, 166p. ISBN 90-8504-209-7

[6] Tilling, A.K., et al., (2006) *Remote sensing to detect nitrogen and water stress in wheat* (http://www.regional.org.au/au/asa/2006/plenary/technology/4584_tillingak.htm), The Australian Society of Agronomy

[7] Werff H. (2006), *Knowledge based remote sensing of complex objects: recognition of spectral and spatial patterns resulting from natural hydrocarbon seepages* (http://www.itc.nl/library/papers_2006/phd/vdwerff.pdf), Utrecht University, ITC Dissertation 131, 138p. ISBN 90-6164-238-8

[8] Noomen, M.F. (2007), *Hyperspectral reflectance of vegetation affected by underground hydrocarbon gas seepage* (http://www.itc.nl/library/papers_2007/phd/noomen.pdf), Enschede, ITC 151p. ISBN 978-90-8504-671-4.

[9] http://www.ittvis.com/ProductServices/ENVI.aspx

[10] http://www.inrim.it/res/hyperspectral_imaging/

[11] http://www.middletonresearch.com

[12] http://photonetc.com/index.php?lan=en&sec=300&sub1=3000&sub2=1023

[13] http://beta.umbio.com/Public%20files/Products/Evince%20Image/EvinceImage.aspx

[14] http://matlabhyperspec.sourceforge.net/

[15] http://www.hyper-cam.com/

Quantum Aspects of Life

Quantum Aspects of Life	
Author	Derek Abbott, Paul C. W. Davies, & Arun K. Pati (Eds.) With foreword by Sir Roger Penrose
Country	UK
Language	English
Subject(s)	Physics and biophysics
Genre(s)	Non-fiction; science text
Publisher	Imperial College Press
Publication date	2008
Pages	581
ISBN	ISBN 978-1-84816-253-2

Quantum Aspects of Life is a science text, with a foreword by Sir Roger Penrose, which notably explores the open question of the role of quantum mechanics at molecular scales of relevance to biology. The book adopts a debate-like style and contains chapters written by various world-experts; giving rise to both a mix of both skeptical and sympathetic viewpoints. The book notably addresses questions of quantum physics, biophysics, nanoscience, quantum chemistry, mathematical biology, complexity theory, and philosophy that are inspired by the 1944 seminal book *What Is Life?* by Erwin Schrödinger.

Contents

- Foreword by Sir Roger Penrose

> **Section 1:** *Emergence and Complexity*

- Chapter 1: "A Quantum Origin of Life?" by Paul C. W. Davies
- Chapter 2: "Quantum Mechanics and Emergence" by Seth Lloyd

> **Section 2:** *Quantum Mechanisms in Biology*

- Chapter 3: "Quantum Coherence and the Search for the First Replicator" by Jim Al-Khalili and Johnjoe McFadden
- Chapter 4: "Ultrafast Quantum Dynamics in Photosynthesis" by Alexandra Olaya-Castro [1], Francesca Fassioli Olsen, Chiu Fan Lee [2], and Neil F. Johnson
- Chapter 5: "Modeling Quantum Decoherence in Biomolecules" by Jacques Bothma, Joel Gilmore, and Ross H. McKenzie

See also

- Quantum biology
- Erwin Schrödinger
- *What Is Life?*

External links

- Book's homepage at ICP [5]

References

[1] http://qwiki.stanford.edu/wiki/Alexandra_Olaya-Castro

[2] http://qwiki.stanford.edu/wiki/Chiu_Fan_Lee

[3] http://qwiki.stanford.edu/wiki/Adrian_P._Flitney

[4] http://qwiki.stanford.edu/wiki/Azhar_Iqbal

[5] http://www.icpress.co.uk/physics/p581.html

Quantum Biochemistry

Quantum chemistry is a branch of theoretical chemistry, which applies quantum mechanics and quantum field theory to address problems in chemistry. The description of the electronic behavior of atoms and molecules as pertaining to their reactivity is one of the applications of quantum chemistry. Quantum chemistry lies on the border between chemistry and physics, and significant contributions have been made by scientists from both fields. It has a strong and active overlap with the field of atomic physics and molecular physics, as well as physical chemistry.

Quantum chemistry mathematically describes the fundamental behavior of matter at the molecular scale.[1] It is, in principle, possible to describe all chemical systems using this theory. In practice, only the simplest chemical systems may realistically be investigated in purely quantum mechanical terms, and approximations must be made for most practical purposes (e.g., Hartree-Fock, post Hartree-Fock or Density functional theory, see computational chemistry for more details). Hence a detailed understanding of quantum mechanics is not necessary for most chemistry, as the important implications of the theory (principally the orbital approximation) can be understood and applied in simpler terms.

In quantum mechanics the Hamiltonian, or the physical state, of a particle can be expressed as the sum of two operators, one corresponding to kinetic energy and the other to potential energy. The Hamiltonian in the Schrödinger wave equation used in quantum chemistry does not contain terms for the spin of the electron.

Solutions of the Schrödinger equation for the hydrogen atom gives the form of the wave function for atomic orbitals, and the relative energy of the various orbitals. The orbital approximation can be used to understand the other atoms e.g. helium, lithium and carbon.

History

The **history of quantum chemistry** essentially began with the 1838 discovery of cathode rays by Michael Faraday, the 1859 statement of the black body radiation problem by Gustav Kirchhoff, the 1877 suggestion by Ludwig Boltzmann that the energy states of a physical system could be discrete, and the 1900 quantum hypothesis by Max Planck that any energy radiating atomic system can theoretically be divided into a number of discrete energy elements ε such that each of these energy elements is proportional to the frequency ν with which they each individually radiate energy, as defined by the following formula:

$$\epsilon = h\nu$$

where h is a numerical value called Planck's Constant. Then, in 1905, to explain the photoelectric effect (1839), i.e., that shining light on certain materials can function to eject electrons from the material, Albert Einstein postulated, based on Planck's quantum hypothesis, that light itself consists of individual quantum particles, which later came to be called photons (1926). In the years to follow, this theoretical basis slowly began to be applied to chemical structure, reactivity, and bonding.

Electronic structure

The first step in solving a quantum chemical problem is usually solving the Schrödinger equation (or Dirac equation in relativistic quantum chemistry) with the electronic molecular Hamiltonian. This is called determining the **electronic structure** of the molecule. It can be said that the electronic structure of a molecule or crystal implies essentially its chemical properties. An exact solution for the Schrödinger equation can only be obtained for the hydrogen atom. Since all other atomic, or molecular systems, involve the motions of three or more "particles", their Schrödinger equations cannot be solved exactly and so approximate solutions must be sought.

Wave model

The foundation of quantum mechanics and quantum chemistry is the **wave model**, in which the atom is a small, dense, positively charged nucleus surrounded by electrons. Unlike the earlier Bohr model of the atom, however, the wave model describes electrons as "clouds" moving in orbitals, and their positions are represented by probability distributions rather than discrete points. The strength of this model lies in its predictive power. Specifically, it predicts the pattern of chemically similar elements found in the periodic table. The wave model is so named because electrons exhibit properties (such as interference) traditionally associated with waves. See wave-particle duality.

Valence bond

Although the mathematical basis of quantum chemistry had been laid by Schrödinger in 1926, it is generally accepted that the first true calculation in quantum chemistry was that of the German physicists Walter Heitler and Fritz London on the hydrogen (H_2) molecule in 1927. Heitler and London's method was extended by the American theoretical physicist John C. Slater and the American theoretical chemist Linus Pauling to become the **Valence-Bond (VB)** [or **Heitler-London-Slater-Pauling (HLSP)**] method. In this method, attention is primarily devoted to the pairwise interactions between atoms, and this method therefore correlates closely with classical chemists' drawings of bonds.

Molecular orbital

An alternative approach was developed in 1929 by Friedrich Hund and Robert S. Mulliken, in which electrons are described by mathematical functions delocalized over an entire molecule. The **Hund-Mulliken** approach or **molecular orbital (MO) method** is less intuitive to chemists, but has turned out capable of predicting spectroscopic properties better than the VB method. This approach is the conceptional basis of the **Hartree-Fock method** and further post Hartree-Fock methods.

Density functional theory

The **Thomas-Fermi model** was developed independently by Thomas and Fermi in 1927. This was the first attempt to describe many-electron systems on the basis of electronic density instead of wave functions, although it was not very successful in the treatment of entire molecules. The method did provide the basis for what is now known as **density functional theory**. Though this method is less developed than post Hartree-Fock methods, its lower computational requirements allow it to tackle larger polyatomic molecules and even macromolecules, which has made it the most used method in computational chemistry at present.

Chemical dynamics

A further step can consist of solving the Schrödinger equation with the total molecular Hamiltonian in order to study the motion of molecules. Direct solution of the Schrödinger equation is called *quantum molecular dynamics*, within the semiclassical approximation *semiclassical molecular dynamics*, and within the classical mechanics framework *molecular dynamics (MD)*. Statistical approaches, using for example Monte Carlo methods, are also possible.

Adiabatic chemical dynamics

In **adiabatic dynamics**, interatomic interactions are represented by single scalar potentials called potential energy surfaces. This is the Born-Oppenheimer approximation introduced by Born and Oppenheimer in 1927. Pioneering applications of this in chemistry were performed by Rice and Ramsperger in 1927 and Kassel in 1928, and generalized into the RRKM theory in 1952 by Marcus who took the transition state theory developed by Eyring in 1935 into account. These methods enable simple estimates of unimolecular reaction rates from a few characteristics of the potential surface.

Non-adiabatic chemical dynamics

Non-adiabatic dynamics consists of taking the interaction between several coupled potential energy surface (corresponding to different electronic quantum states of the molecule). The coupling terms are called **vibronic couplings**. The pioneering work in this field was done by Stueckelberg, Landau, and Zener in the 1930s, in their work on what is now known as the Landau-Zener transition. Their formula allows the transition probability between two diabatic potential curves in the neighborhood of an avoided crossing to be calculated.

Quantum chemistry and quantum field theory

The application of quantum field theory (QFT) to chemical systems and theories has become increasingly common in the modern physical sciences. One of the first and most fundamentally explicit appearances of this is seen in the theory of the photomagneton. In this system, plasmas, which are ubiquitous in both physics and chemistry, are studied in order to determine the basic quantization of the underlying bosonic field. However, quantum field theory is of interest in many fields of chemistry, including: nuclear chemistry, astrochemistry, sonochemistry, and quantum hydrodynamics. Field theoretic methods have also been critical in developing the ab initio Effective Hamiltonian theory of semi-empirical pi-electron methods.

See also

- Atomic physics
- Computational chemistry
- Condensed matter physics
- International Academy of Quantum Molecular Science
- Molecular modelling
- Physical chemistry
- Quantum chemistry computer programs
- Quantum electrochemistry
- QMC@Home
- Theoretical physics

Further reading

- Atkins, P.W. Friedman, R. (2005). *Molecular Quantum Mechanics* , Oxford University Press, 4th edition. ISBN 978-0199274987
- Atkins, P.W. *Physical Chemistry* (Oxford University Press) ISBN 0-19-879285-9
- Atkins, P.W. Friedman, R. (2008). *Quanta, Matter and Change: A Molecular Approach to Physical Change* , W. H. Freeman. ISBN 978-0716761174
- Bernard Pullman and Alberte Pullman. 1963. *Quantum Biochemistry*, New York and London: Academic Press.
- Eric R. Scerri, The Periodic Table: Its Story and Its Significance, Oxford University Press, 2006. Considers the extent to which chemistry and especially the periodic system has been reduced to quantum mechanics. ISBN 0-19-530573-6.
- McWeeny, R. *Coulson's Valence* (Oxford Science Publications) ISBN 0-19-855144-4
- Karplus M., Porter R.N. (1971). *Atoms and Molecules. An introduction for students of physical chemistry* , Benjamin-Cummings Publishing Company, ISBN 978-0805352184
- Landau, L.D. and Lifshitz, E.M. *Quantum Mechanics:Non-relativistic Theory* (Course of Theoretical Physics vol.3) (Pergamon Press)
- Levine, I. (2008). *Physical Chemistry* , McGraw-Hill Science, 6th edition. ISBN 978-0072538625 (Hardcover) or ISBN 978-0071276368 (Paperback)

- Pauling, L. (1954). *General Chemistry*. Dover Publications. ISBN 0-486-65622-5.
- Pauling, L., and Wilson, E. B. *Introduction to Quantum Mechanics with Applications to Chemistry* (Dover Publications) ISBN 0-486-64871-0
- Simon, Z. 1976. *Quantum Biochemistry and Specific Interactions.*, Taylor & Francis; ISBN 978-0856260872 and ISBN 0-85-6260878 .

External links

- The Sherrill Group - Notes [2]
- ChemViz Curriculum Support Resources [3]
- Early ideas in the history of quantum chemistry [4]
- The Particle Adventure [5]

Nobel lectures by quantum chemists

- Walter Kohn's Nobel lecture [6]
- Rudolph Marcus' Nobel lecture [7]
- Robert Mulliken's Nobel lecture [8]
- Linus Pauling's Nobel lecture [9]
- John Pople's Nobel lecture [10]

References

[1] "Quantum Chemistry" (http://cmm.cit.nih.gov/modeling/guide_documents/quantum_mechanics_document.html). *The NIH Guide to Molecular Modeling*. National Institutes of Health. . Retrieved 2007-09-08.

[2] http://vergil.chemistry.gatech.edu/notes/index.html

[3] http://www.shodor.org/chemviz/

[4] http://www.quantum-chemistry-history.com/

[5] http://particleadventure.org/

[6] http://nobelprize.org/chemistry/laureates/1998/kohn-lecture.html

[7] http://nobelprize.org/chemistry/laureates/1992/marcus-lecture.html

[8] http://nobelprize.org/chemistry/laureates/1966/mulliken-lecture.html

[9] http://nobelprize.org/chemistry/laureates/1954/pauling-lecture.html

[10] http://nobelprize.org/chemistry/laureates/1998/pople-lecture.html

Nucleic Acids and Molecular Biology

DNA

Deoxyribonucleic acid (**DNA**) is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms and some viruses. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints or a recipe, or a code, since it contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.

Chemically, DNA consists of two long polymers of simple units called nucleotides, with backbones made of sugars and phosphate groups joined by ester bonds. These two strands run in opposite directions to each other and are therefore anti-parallel. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This information is read using the genetic code, which specifies the sequence of the amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription.

The structure of part of a DNA double helix

Within cells, DNA is organized into long structures called chromosomes. These chromosomes are duplicated before cells divide, in a process called DNA replication. Eukaryotic organisms (animals, plants, fungi, and protists) store most of their DNA inside the cell nucleus and some of their DNA in organelles, such as mitochondria or chloroplasts.[1] In contrast, prokaryotes (bacteria and archaea) store their DNA only in the cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA. These compact structures guide the interactions between DNA and other proteins, helping control which parts of the DNA are transcribed.

This article is part of the series on:

Gene expression

a Molecular biology topic (*portal*)

(Glossary)

Introduction to Genetics
General flow: DNA > RNA > Protein
special transfers (RNA > RNA, RNA > DNA, Protein > Protein)
Genetic code
Transcription
Transcription (*Transcription factors*, *RNA Polymerase*,*promoter*) Prokaryotic / Archaeal / Eukaryotic
post-transcriptional modification (*hnRNA*,*Splicing*)
Translation
Translation (*Ribosome*,*tRNA*) Prokaryotic / Archaeal / Eukaryotic
post-translational modification (*functional groups, peptides, structural changes*)
gene regulation
epigenetic regulation (*Genomic imprinting*)
transcriptional regulation
post-transcriptional regulation (*sequestration*, *alternative splicing*,*miRNA*)
translational regulation
post-translational regulation (*reversible*,*irreversible*)
ask a question [2] , edit [3]

Properties

DNA is a long polymer made from repeating units called nucleotides.[4] [5] [6] The DNA chain is 22 to 26 Ångströms wide (2.2 to 2.6 nanometres), and one nucleotide unit is 3.3 Å (0.33 nm) long.[7] Although each individual repeating unit is very small, DNA polymers can be very large molecules containing millions of nucleotides. For instance, the largest human chromosome, chromosome number 1, is approximately 220 million base pairs long.[8]

In living organisms, DNA does not usually exist as a single molecule, but instead as a pair of molecules that are held tightly together.[9] [10] These two long strands entwine like vines, in the shape of a double helix. The nucleotide repeats contain both the segment of the backbone of the molecule, which holds the chain together, and a base, which interacts with the other DNA strand in the helix. A base linked to a sugar is

Chemical structure of DNA. Hydrogen bonds shown as dotted lines.

called a nucleoside and a base linked to a sugar and one or more phosphate groups is called a nucleotide. If multiple nucleotides are linked together, as in DNA, this polymer is called a polynucleotide.[11]

The backbone of the DNA strand is made from alternating phosphate and sugar residues.[12] The sugar in DNA is 2-deoxyribose, which is a pentose (five-carbon) sugar. The sugars are joined together by phosphate groups that form phosphodiester bonds between the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean a strand of DNA has a direction. In a double helix the direction of the nucleotides in one strand is opposite to their direction in the other strand: the strands are *antiparallel*. The asymmetric ends of DNA strands are called the 5′ (*five prime*) and 3′ (*three prime*) ends, with the 5' end having a terminal phosphate group and the 3' end a terminal hydroxyl group. One major difference between DNA and RNA is the sugar, with the 2-deoxyribose in DNA being replaced by the alternative pentose sugar ribose in RNA.[10]
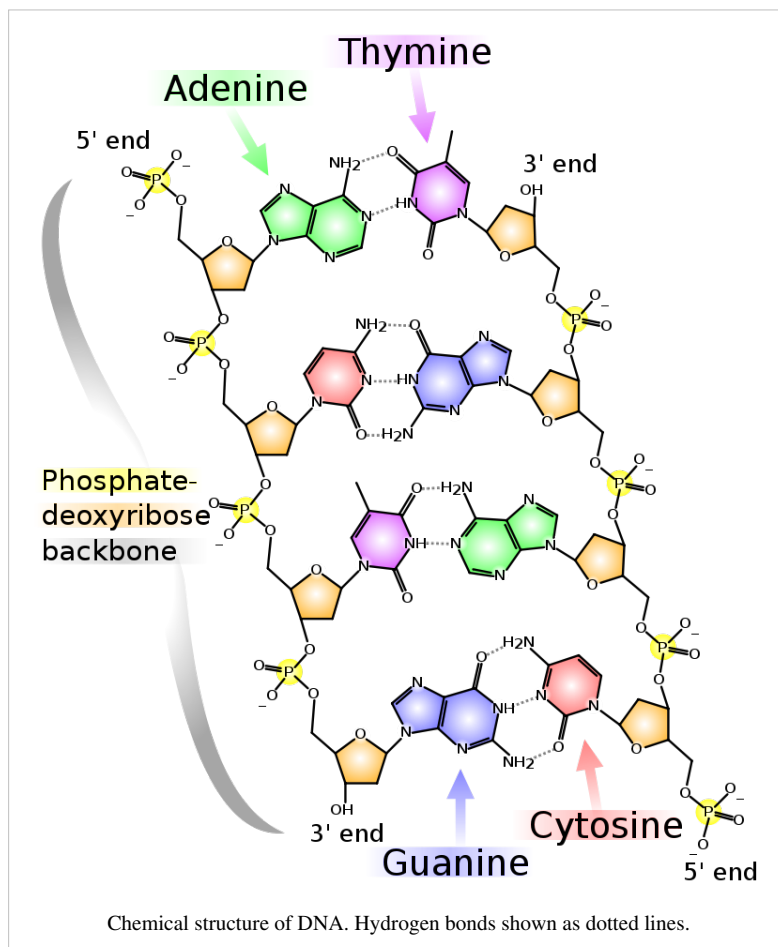
The DNA double helix is stabilized by hydrogen bonds between the bases attached to the two strands. The four bases found in DNA are adenine (abbreviated A), cytosine (C), guanine (G) and thymine (T). These four bases are attached to the sugar/phosphate to form the complete nucleotide, as shown for adenosine monophosphate.

These bases are classified into two types; adenine and guanine are fused five- and six-membered heterocyclic compounds called purines, while cytosine and thymine are six-membered rings called pyrimidines.[10] A fifth pyrimidine base, called uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking a methyl group on its ring. Uracil is not usually found in DNA, occurring only as a breakdown product of cytosine. In addition to RNA and DNA, a large number of artificial nucleic acid analogues have also been created to study the proprieties of nucleic acids, or for use in biotechnology.[14]

Grooves

Twin helical strands form the DNA backbone. Another double helix may be found by tracing the spaces, or grooves, between the strands. These voids are adjacent to the base pairs and may provide a binding site. As the strands are not directly opposite each other, the grooves are unequally sized. One groove, the major groove, is 22 Å wide and the other, the minor groove, is 12 Å wide.[15] The narrowness of the minor groove means that the edges of the bases are more accessible in the major groove. As a result, proteins like

A section of DNA. The bases lie horizontally between the two spiraling strands.[13] Animated version at File:DNA orbit animated.gif.

transcription factors that can bind to specific sequences in double-stranded DNA usually make contacts to the sides of the bases exposed in the major groove.[16] This situation varies in unusual conformations of DNA within the cell *(see below)*, but the major and minor grooves are always named to reflect the differences in size that would be seen if the DNA is twisted back into the ordinary B form.

Base pairing

Each type of base on one strand forms a bond with just one type of base on the other strand. This is called complementary base pairing. Here, purines form hydrogen bonds to pyrimidines, with A bonding only to T, and C bonding only to G. This arrangement of two nucleotides binding together across the double helix is called a base pair. As hydrogen bonds are not covalent, they can be broken and rejoined relatively easily. The two strands of DNA in a double helix can therefore be pulled apart like a zipper, either by a mechanical force or high temperature.[17] As a result of this complementarity, all the information in the double-stranded sequence of a DNA helix is duplicated on each strand, which is vital in DNA replication. Indeed, this reversible and specific interaction between complementary base pairs is critical for all the functions of DNA in living organisms.[5]

Top, a **GC** base pair with three hydrogen bonds. Bottom, an **AT** base pair with two hydrogen bonds. Non-covalent hydrogen bonds between the pairs are shown as dashed lines.

The two types of base pairs form different numbers of hydrogen bonds, AT forming two hydrogen bonds, and GC forming three hydrogen bonds (see figures, left). DNA with high GC-content is more stable than DNA with low GC-content, but contrary to popular belief, this is not due to the extra hydrogen bond of a GC base pair but rather the contribution of stacking interactions (hydrogen bonding merely provides specificity of the pairing, not stability).[18] As a result, it is both the percentage of GC base pairs and the overall length of a DNA double helix that determine the strength of the association between the two strands of DNA. Long DNA helices with a high GC content have stronger-interacting strands, while short helices with high AT content have weaker-interacting strands.[19] In biology, parts of the DNA double helix that need to separate easily, such as the TATAAT Pribnow box in some promoters, tend to have a high AT content, making the strands easier to pull apart.[20] In the laboratory, the strength of this interaction can be measured by finding the temperature required to break the hydrogen bonds, their melting temperature (also called T_m value). When all the base pairs in a DNA double helix melt, the strands separate and exist in solution as two entirely independent molecules. These single-stranded DNA molecules have no single common shape, but some conformations are more stable than others.[21]

Sense and antisense

A DNA sequence is called "sense" if its sequence is the same as that of a messenger RNA copy that is translated into protein.[22] The sequence on the opposite strand is called the "antisense" sequence. Both sense and antisense sequences can exist on different parts of the same strand of DNA (i.e. both strands contain both sense and antisense sequences). In both prokaryotes and eukaryotes, antisense RNA sequences are produced, but the functions of these RNAs are not entirely clear.[23] One proposal is that antisense RNAs are involved in regulating gene expression through RNA-RNA base pairing.[24]

A few DNA sequences in prokaryotes and eukaryotes, and more in plasmids and viruses, blur the distinction between sense and antisense strands by having overlapping genes.[25] In these cases, some DNA sequences do double duty, encoding one protein when read along one strand, and a second protein when read in the opposite direction along the other strand. In bacteria, this overlap may be involved in the regulation of gene transcription,[26] while in viruses, overlapping genes increase the amount of information that can be encoded within the small viral genome.[27]

Supercoiling

DNA can be twisted like a rope in a process called DNA supercoiling. With DNA in its "relaxed" state, a strand usually circles the axis of the double helix once every 10.4 base pairs, but if the DNA is twisted the strands become more tightly or more loosely wound.[28] If the DNA is twisted in the direction of the helix, this is positive supercoiling, and the bases are held more tightly together. If they are twisted in the opposite direction, this is negative supercoiling, and the bases come apart more easily. In nature, most DNA has slight negative supercoiling that is introduced by enzymes called topoisomerases.[29] These enzymes are also needed to relieve the twisting

stresses introduced into DNA strands during processes such as transcription and DNA replication.[30]

Alternate DNA structures

DNA exists in many possible conformations that include A-DNA, B-DNA, and Z-DNA forms, although, only B-DNA and Z-DNA have been directly observed in functional organisms.[12] The conformation that DNA adopts depends on the hydration level, DNA sequence, the amount and direction of supercoiling, chemical modifications of the bases, the type and concentration of metal ions, as well as the presence of polyamines in solution.[31]

From left to right, the structures of A, B and Z DNA
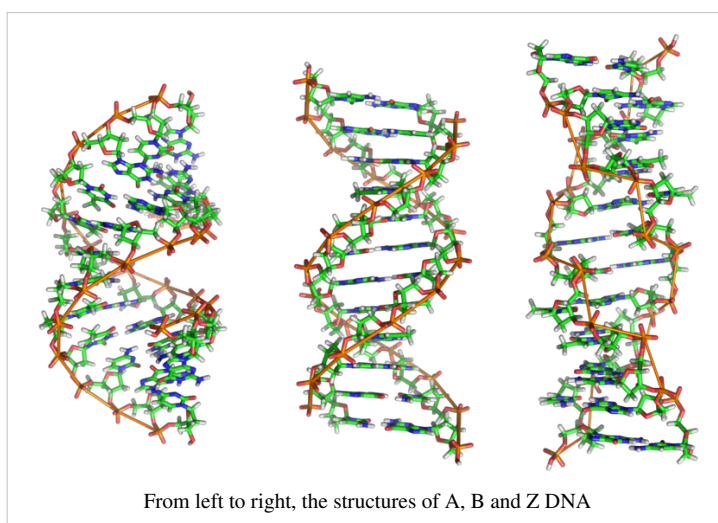
The first published reports of A-DNA X-ray diffraction patterns— and also B-DNA used analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA.[32] [33] An alternate analysis was then proposed by Wilkins *et al.*, in 1953, for the *in vivo* B-DNA X-ray diffraction/scattering patterns of highly hydrated DNA fibers in terms of squares of Bessel functions.[34] In the same journal, Watson and Crick presented their molecular modeling analysis of the DNA X-ray diffraction patterns to suggest that the structure was a double-helix.[9]

Although the `B-DNA form' is most common under the conditions found in cells,[35] it is not a well-defined conformation but a family of related DNA conformations[36] that occur at the high hydration levels present in living cells. Their corresponding X-ray diffraction and scattering patterns are characteristic of molecular paracrystals with a significant degree of disorder.[37] [38]

Compared to B-DNA, the A-DNA form is a wider right-handed spiral, with a shallow, wide minor groove and a narrower, deeper major groove. The A form occurs under non-physiological conditions in partially dehydrated samples of DNA, while in the cell it may be produced in hybrid pairings of DNA and RNA strands, as well as in enzyme-DNA complexes.[39] [40] Segments of DNA where the bases have been chemically modified by methylation may undergo a larger change in conformation and adopt the Z form. Here, the strands turn about the helical axis in a left-handed spiral, the opposite of the more common B form.[41] These unusual structures can be recognized by specific Z-DNA binding proteins and may be involved in the regulation of transcription.[42]

DNA quadruplex formed by telomere repeats. The looped conformation of the DNA backbone is very different from the typical DNA helix.[43]
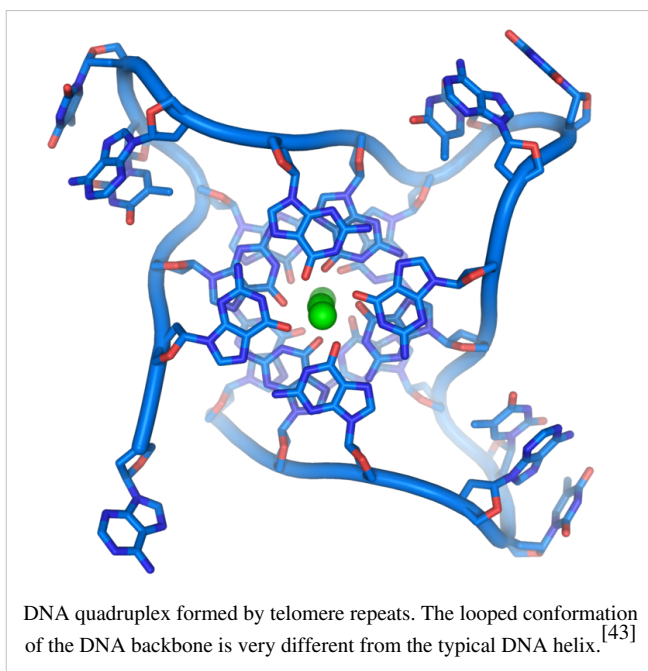
Quadruplex structures

At the ends of the linear chromosomes are specialized regions of DNA called telomeres. The main function of these regions is to allow the cell to replicate chromosome ends using the enzyme telomerase, as the enzymes that normally replicate DNA cannot copy the extreme 3′ ends of chromosomes.[44] These specialized chromosome caps also help protect the DNA ends, and stop the DNA repair systems in the cell from treating them as damage to be corrected.[45] In human cells, telomeres are usually lengths of single-stranded DNA containing several thousand repeats of a simple TTAGGG sequence.[46]

These guanine-rich sequences may stabilize chromosome ends by forming structures of stacked sets of four-base units, rather than the usual base pairs found in other DNA molecules. Here, four guanine bases form a flat plate and these flat four-base units then stack on top of each other, to form a stable *G-quadruplex* structure.[47] These structures are stabilized by hydrogen bonding between the edges of the bases and chelation of a metal ion in the centre of each four-base unit.[48] Other structures can also be formed, with the central set of four bases coming from either a single strand folded around the bases, or several different parallel strands, each contributing one base to the central structure.

In addition to these stacked structures, telomeres also form large loop structures called telomere loops, or T-loops. Here, the single-stranded DNA curls around in a long circle stabilized by telomere-binding proteins.[49] At the very end of the T-loop, the single-stranded telomere DNA is held onto a region of double-stranded DNA by the telomere strand disrupting the double-helical DNA and base pairing to one of the two strands. This triple-stranded structure is called a displacement loop or D-loop.[47]

| Single branch | Multiple branches |
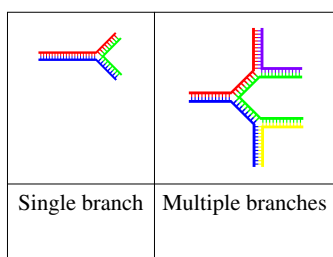
Branched DNA can form networks containing multiple branches.

Branched DNA

In DNA fraying occurs when non-complementary regions exist at the end of an otherwise complementary double-strand of DNA. However, branched DNA can occur if a third strand of DNA is introduced and contains adjoining regions able to hybridize with the frayed regions of the pre-existing double-strand. Although the simplest example of branched DNA involves only three strands of DNA, complexes involving additional strands and multiple branches are also possible.[50] Branched DNA can be used in nanotechnology to construct geometric shapes, see the section on uses in technology below.

Chemical modifications

| cytosine | 5-methylcytosine | thymine |
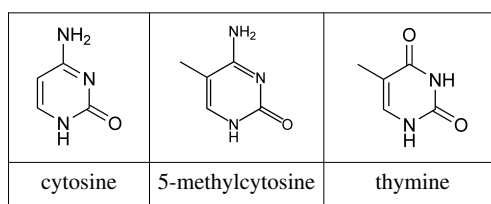
Structure of cytosine with and without the 5-methyl group. Deamination converts 5-methylcytosine into thymine.

Base modifications

The expression of genes is influenced by how the DNA is packaged in chromosomes, in a structure called chromatin. Base modifications can be involved in packaging, with regions that have low or no gene expression usually containing high levels of methylation of cytosine bases. For example, cytosine methylation, produces 5-methylcytosine, which is important for X-chromosome inactivation.[51] The average level of methylation varies between organisms - the worm *Caenorhabditis elegans* lacks cytosine methylation, while vertebrates have higher levels, with up to 1% of their DNA containing 5-methylcytosine.[52] Despite the importance of 5-methylcytosine, it can deaminate to leave a thymine base, methylated cytosines are therefore particularly prone to mutations.[53] Other base modifications include adenine methylation in bacteria, the presence of 5-hydroxymethylcytosine in the brain,[54] and the glycosylation of uracil to produce the "J-base" in kinetoplastids.[55] [56]

Damage

DNA can be damaged by many sorts of mutagens, which change the DNA sequence. Mutagens include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays. The type of DNA damage produced depends on the type of mutagen. For example, UV light can damage DNA by producing thymine dimers, which are cross-links between pyrimidine bases.[58] On the other hand, oxidants such as free radicals or hydrogen peroxide produce multiple forms of damage, including base modifications, particularly of guanosine, and double-strand breaks.[59] A typical human cell contains about 150,000 bases that have suffered oxidative damage.[60] Of these oxidative lesions, the most dangerous are double-strand breaks, as these are difficult to repair and can produce point mutations, insertions and deletions from the DNA sequence, as well as chromosomal translocations.[61]

Many mutagens fit into the space between two adjacent base pairs, this is called *intercalating*. Most intercalators are aromatic and planar molecules, and include Ethidium bromide, daunomycin, and
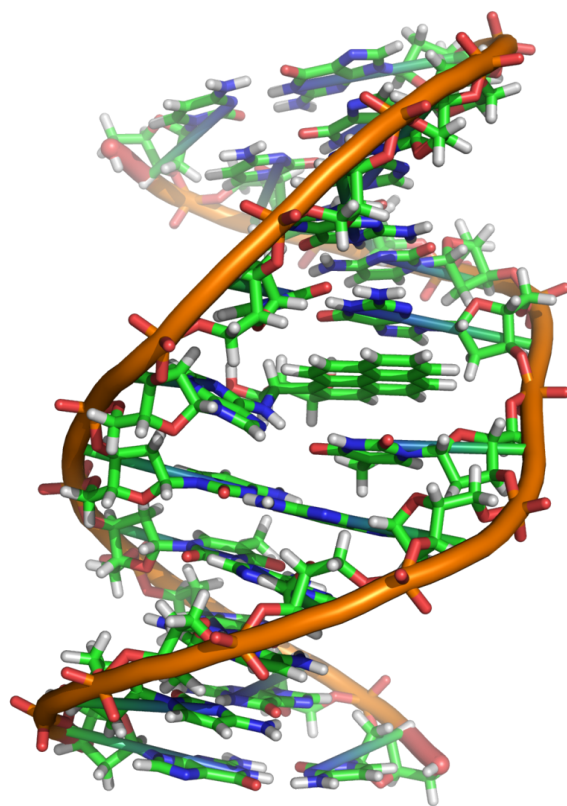
A covalent adduct between benzo[*a*]pyrene, the major mutagen in tobacco smoke, and DNA[57]

doxorubicin. In order for an intercalator to fit between base pairs, the bases must separate, distorting the DNA strands by unwinding of the double helix. This inhibits both transcription and DNA replication, causing toxicity and mutations. As a result, DNA intercalators are often carcinogens, and Benzo[*a*]pyrene diol epoxide, acridines, aflatoxin and ethidium bromide are well-known examples.[62] [63] [64] Nevertheless, due to their ability to inhibit DNA transcription and replication, other similar toxins are also used in chemotherapy to inhibit rapidly growing cancer cells.[65]

Biological functions

DNA usually occurs as linear chromosomes in eukaryotes, and circular chromosomes in prokaryotes. The set of chromosomes in a cell makes up its genome; the human genome has approximately 3 billion base pairs of DNA arranged into 46 chromosomes.[66] The information carried by DNA is held in the sequence of pieces of DNA called genes. Transmission of genetic information in genes is achieved via complementary base pairing. For example, in transcription, when a cell uses the information in a gene, the DNA sequence is copied into a complementary RNA sequence through the attraction between the DNA and the correct RNA nucleotides. Usually, this RNA copy is then used to make a matching protein sequence in a process called translation which depends on the same interaction between RNA nucleotides. Alternatively, a cell may simply copy its genetic information in a process called DNA replication. The details of these functions are covered in other articles; here we focus on the interactions between DNA and other molecules that mediate the function of the genome.

Genes and genomes

Genomic DNA is located in the cell nucleus of eukaryotes, as well as small amounts in mitochondria and chloroplasts. In prokaryotes, the DNA is held within an irregularly shaped body in the cytoplasm called the nucleoid.[67] The genetic information in a genome is held within genes, and the complete set of this information in an organism is called its genotype. A gene is a unit of heredity and is a region of DNA that influences a particular characteristic in an organism. Genes contain an open reading frame that can be transcribed, as well as regulatory sequences such as promoters and enhancers, which control the transcription of the open reading frame.

In many species, only a small fraction of the total sequence of the genome encodes protein. For example, only about 1.5% of the human genome consists of protein-coding exons, with over 50% of human DNA consisting of non-coding repetitive sequences.[68] The reasons for the presence of so much non-coding DNA in eukaryotic genomes and the extraordinary differences in genome size, or *C-value*, among species represent a long-standing puzzle known as the "C-value enigma."[69] However, DNA sequences that do not code protein may still encode functional non-coding RNA molecules, which are involved in the regulation of gene expression.[70]

T7 RNA polymerase (blue) producing a mRNA (green) from a DNA template (orange).[71]
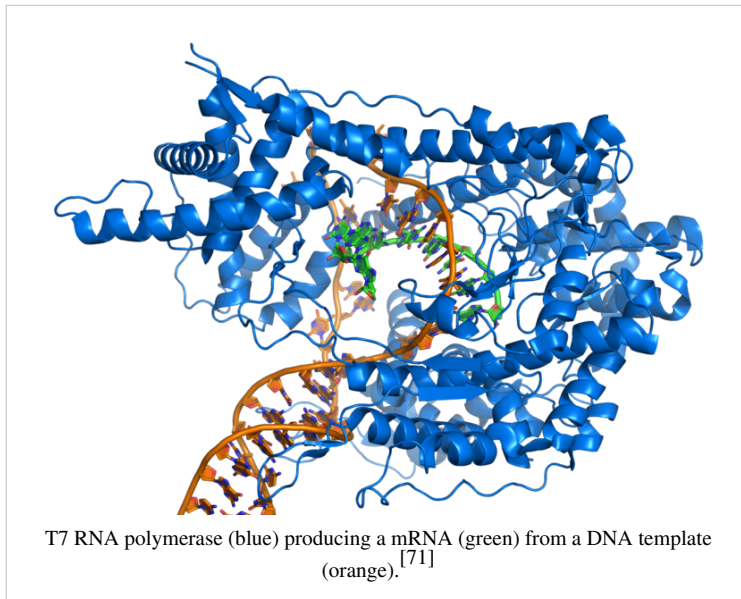
Some non-coding DNA sequences play structural roles in chromosomes. Telomeres and centromeres typically contain few genes, but are important for the function and stability of chromosomes.[45] [72] An abundant form of non-coding DNA in humans are pseudogenes, which are copies of genes that have been disabled by mutation.[73] These sequences are usually just molecular fossils, although they can occasionally serve as raw genetic material for the creation of new genes through the process of gene duplication and divergence.[74]

Transcription and translation

A gene is a sequence of DNA that contains genetic information and can influence the phenotype of an organism. Within a gene, the sequence of bases along a DNA strand defines a messenger RNA sequence, which then defines one or more protein sequences. The relationship between the nucleotide sequences of genes and the amino-acid sequences of proteins is determined by the rules of translation, known collectively as the genetic code. The genetic code consists of three-letter 'words' called *codons* formed from a sequence of three nucleotides (e.g. ACT, CAG, TTT).

In transcription, the codons of a gene are copied into messenger RNA by RNA polymerase. This RNA copy is then decoded by a ribosome that reads the RNA sequence by base-pairing the messenger RNA to transfer RNA, which carries amino acids. Since there are 4 bases in 3-letter combinations, there are 64 possible codons (4^3 combinations). These encode the twenty standard amino acids, giving most amino acids more than one possible codon. There are also three 'stop' or 'nonsense' codons signifying the end of the coding region; these are the TAA, TGA and TAG codons.

Replication

Cell division is essential for an organism to grow, but when a cell divides it must replicate the DNA in its genome so that the two daughter cells have the same genetic information as their parent. The double-stranded structure of DNA provides a simple mechanism for DNA replication. Here, the two strands are separated and then each strand's complementary DNA sequence is recreated by an enzyme called DNA polymerase. This enzyme makes the complementary strand by

DNA replication. The double helix is unwound by a helicase and topoisomerase. Next, one DNA polymerase produces the leading strand copy. Another DNA polymerase binds to the lagging strand. This enzyme makes discontinuous segments (called Okazaki fragments) before DNA ligase joins them together.
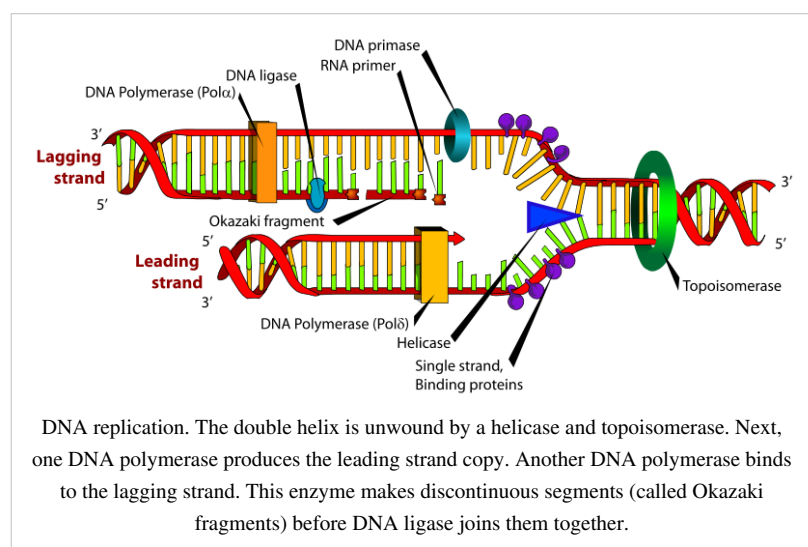
finding the correct base through complementary base pairing, and bonding it onto the original strand. As DNA polymerases can only extend a DNA strand in a 5′ to 3′ direction, different mechanisms are used to copy the

antiparallel strands of the double helix.[75] In this way, the base on the old strand dictates which base appears on the new strand, and the cell ends up with a perfect copy of its DNA.

Interactions with proteins

All the functions of DNA depend on interactions with proteins. These protein interactions can be non-specific, or the protein can bind specifically to a single DNA sequence. Enzymes can also bind to DNA and of these, the polymerases that copy the DNA base sequence in transcription and DNA replication are particularly important.

DNA-binding proteins
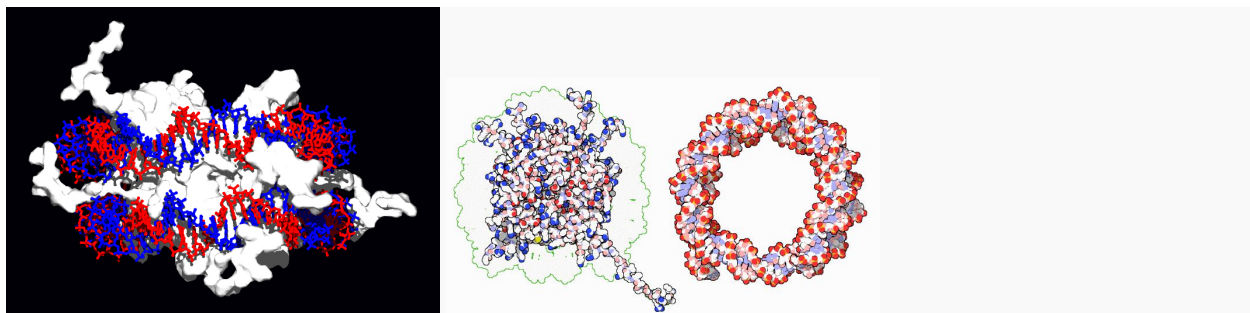
Interaction of DNA with histones (shown in white, top). These proteins' basic amino acids (below left, blue) bind to the acidic phosphate groups on DNA (below right, red).

Structural proteins that bind DNA are well-understood examples of non-specific DNA-protein interactions. Within chromosomes, DNA is held in complexes with structural proteins. These proteins organize the DNA into a compact structure called chromatin. In eukaryotes this structure involves DNA binding to a complex of small basic proteins called histones, while in prokaryotes multiple types of proteins are involved.[76] [77] The histones form a disk-shaped complex called a nucleosome, which contains two complete turns of double-stranded DNA wrapped around its surface. These non-specific interactions are formed through basic residues in the histones making ionic bonds to the acidic sugar-phosphate backbone of the DNA, and are therefore largely independent of the base sequence.[78] Chemical modifications of these basic amino acid residues include methylation, phosphorylation and acetylation.[79] These chemical changes alter the strength of the interaction between the DNA and the histones, making the DNA more or less accessible to transcription factors and changing the rate of transcription.[80] Other non-specific DNA-binding proteins in chromatin include the high-mobility group proteins, which bind to bent or distorted DNA.[81] These proteins are important in bending arrays of nucleosomes and arranging them into the larger structures that make up chromosomes.[82]

A distinct group of DNA-binding proteins are the DNA-binding proteins that specifically bind single-stranded DNA. In humans, replication protein A is the best-understood member of this family and is used in processes where the double helix is separated, including DNA replication, recombination and DNA repair.[83] These binding proteins seem to stabilize single-stranded DNA and protect it from forming stem-loops or being degraded by nucleases.

In contrast, other proteins have evolved to bind to particular DNA sequences. The most intensively studied of these are the various transcription factors, which are proteins that regulate transcription. Each transcription factor binds to one particular set of DNA sequences and activates or inhibits the transcription of genes that have these sequences close to their promoters. The transcription factors do this in two ways. Firstly, they can bind the RNA polymerase responsible for transcription, either directly or through other mediator proteins; this locates the polymerase at the promoter and allows it to begin transcription.[85] Alternatively, transcription factors can bind enzymes that modify the histones at the promoter; this will change the accessibility of the DNA template to the polymerase.[86]

As these DNA targets can occur throughout an organism's genome, changes in the activity of one type of transcription factor can affect thousands of genes.[87] Consequently, these proteins are often the targets of the signal transduction processes that control responses to environmental changes or cellular differentiation and development. The specificity of these transcription factors' interactions with DNA come from the proteins making multiple contacts to the edges of the DNA bases, allowing them to "read" the DNA sequence. Most of these base-interactions are made in the major groove, where the bases are most accessible.[88]

The lambda repressor helix-turn-helix transcription factor bound to its DNA target[84]

The restriction enzyme EcoRV (green) in a complex with its substrate DNA[89]
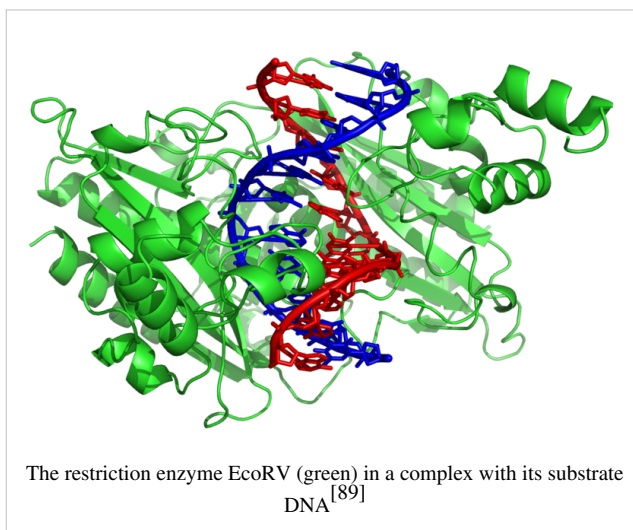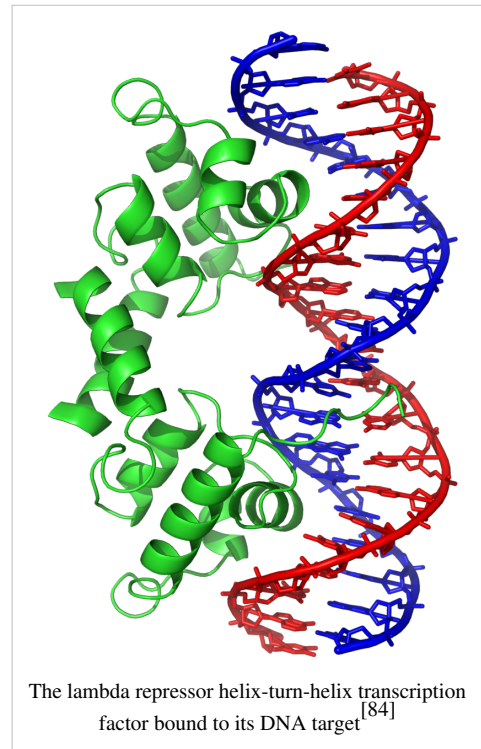
DNA-modifying enzymes

Nucleases and ligases

Nucleases are enzymes that cut DNA strands by catalyzing the hydrolysis of the phosphodiester bonds. Nucleases that hydrolyse nucleotides from the ends of DNA strands are called exonucleases, while endonucleases cut within strands. The most frequently used nucleases in molecular biology are the restriction endonucleases, which cut DNA at specific sequences. For instance, the EcoRV enzyme shown to the left recognizes the 6-base sequence 5′-GAT|ATC-3′ and makes a cut at the vertical line. In nature, these enzymes protect bacteria against phage infection by digesting the phage DNA when it enters the bacterial cell, acting as part of the restriction modification system.[90] In technology, these sequence-specific nucleases are used in molecular cloning and DNA fingerprinting.

Enzymes called DNA ligases can rejoin cut or broken DNA strands.[91] Ligases are particularly important in lagging strand DNA replication, as they join together the short segments of DNA produced at the replication fork into a complete copy of the DNA template. They are also used in DNA repair and genetic recombination.[91]

Topoisomerases and helicases

Topoisomerases are enzymes with both nuclease and ligase activity. These proteins change the amount of supercoiling in DNA. Some of these enzymes work by cutting the DNA helix and allowing one section to rotate, thereby reducing its level of supercoiling; the enzyme then seals the DNA break.[29] Other types of these enzymes are capable of cutting one DNA helix and then passing a second strand of DNA through this break, before rejoining the helix.[92] Topoisomerases are required for many processes involving DNA, such as DNA replication and transcription.[30]

Helicases are proteins that are a type of molecular motor. They use the chemical energy in nucleoside triphosphates, predominantly ATP, to break hydrogen bonds between bases and unwind the DNA double helix into single strands.[93] These enzymes are essential for most processes where enzymes need to access the DNA bases.

Polymerases

Polymerases are enzymes that synthesize polynucleotide chains from nucleoside triphosphates. The sequence of their products are copies of existing polynucleotide chains - which are called *templates*. These enzymes function by adding nucleotides onto the 3′ hydroxyl group of the previous nucleotide in a DNA strand. Consequently, all polymerases work in a 5′ to 3′ direction.[94] In the active site of these enzymes, the incoming nucleoside triphosphate base-pairs to the template: this allows polymerases to accurately synthesize the complementary strand of their template. Polymerases are classified according to the type of template that they use.

In DNA replication, a DNA-dependent DNA polymerase makes a copy of a DNA sequence. Accuracy is vital in this process, so many of these polymerases have a proofreading activity. Here, the polymerase recognizes the occasional mistakes in the synthesis reaction by the lack of base pairing between the mismatched nucleotides. If a mismatch is detected, a 3′ to 5′ exonuclease activity is activated and the incorrect base removed.[95] In most organisms DNA polymerases function in a large complex called the replisome that contains multiple accessory subunits, such as the DNA clamp or helicases.[96]

RNA-dependent DNA polymerases are a specialized class of polymerases that copy the sequence of an RNA strand into DNA. They include reverse transcriptase, which is a viral enzyme involved in the infection of cells by retroviruses, and telomerase, which is required for the replication of telomeres.[44] [97] Telomerase is an unusual polymerase because it contains its own RNA template as part of its structure.[45]

Transcription is carried out by a DNA-dependent RNA polymerase that copies the sequence of a DNA strand into RNA. To begin transcribing a gene, the RNA polymerase binds to a sequence of DNA called a promoter and separates the DNA strands. It then copies the gene sequence into a messenger RNA transcript until it reaches a region of DNA called the terminator, where it halts and detaches from the DNA. As with human DNA-dependent DNA polymerases, RNA polymerase II, the enzyme that transcribes most of the genes in the human genome, operates as part of a large protein complex with multiple regulatory and accessory subunits.[98]

Genetic recombination
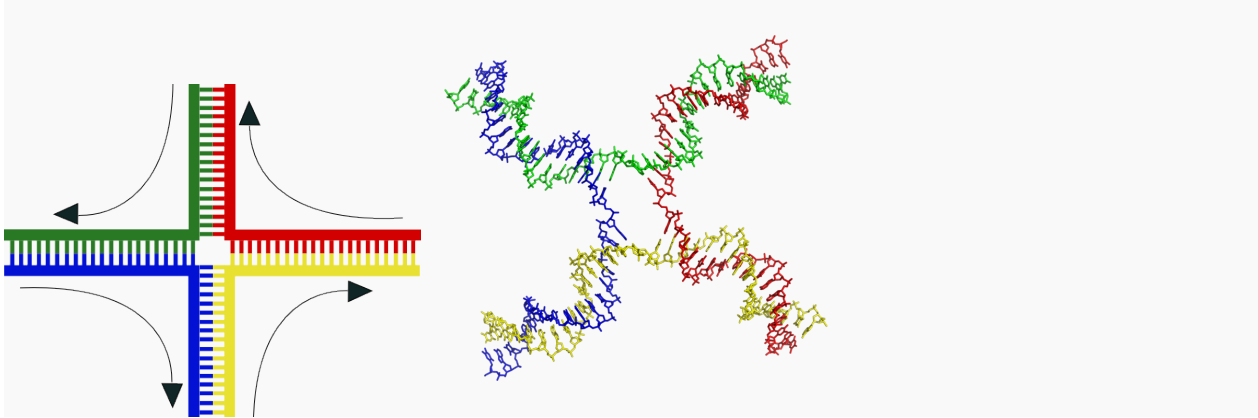
Structure of the Holliday junction intermediate in genetic recombination. The four separate DNA strands are coloured red, blue, green and yellow.[99]

Recombination involves the breakage and rejoining of two chromosomes (M and F) to produce two re-arranged chromosomes (C1 and C2).
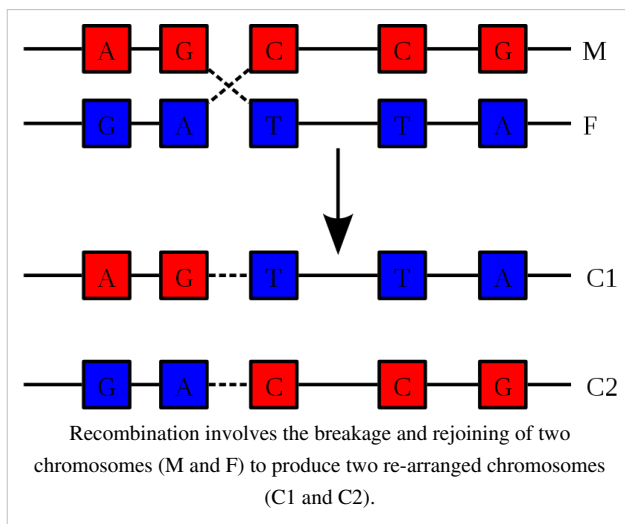
A DNA helix usually does not interact with other segments of DNA, and in human cells the different chromosomes even occupy separate areas in the nucleus called "chromosome territories".[100] This physical separation of different chromosomes is important for the ability of DNA to function as a stable repository for information, as one of the few times chromosomes interact is during chromosomal crossover when they recombine. Chromosomal crossover is when two DNA helices break, swap a section and then rejoin.

Recombination allows chromosomes to exchange genetic information and produces new combinations of genes, which increases the efficiency of natural selection and can be important in the rapid evolution of new proteins.[101] Genetic recombination can also be involved in DNA repair, particularly in the cell's response to double-strand breaks.[102]

The most common form of chromosomal crossover is homologous recombination, where the two chromosomes involved share very similar sequences. Non-homologous recombination can be damaging to cells, as it can produce chromosomal translocations and genetic abnormalities. The recombination reaction is catalyzed by enzymes known as recombinases, such as RAD51.[103] The first step in recombination is a double-stranded break either caused by an endonuclease or damage to the DNA.[104] A series of steps catalyzed in part by the recombinase then leads to joining of the two helices by at least one Holliday junction, in which a segment of a single strand in each helix is annealed to the complementary strand in the other helix. The Holliday junction is a tetrahedral junction structure that can be moved along the pair of chromosomes, swapping one strand for another. The recombination reaction is then halted by cleavage of the junction and re-ligation of the released DNA.[105]

Evolution

DNA contains the genetic information that allows all modern living things to function, grow and reproduce. However, it is unclear how long in the 4-billion-year history of life DNA has performed this function, as it has been proposed that the earliest forms of life may have used RNA as their genetic material.[94] [106] RNA may have acted as the central part of early cell metabolism as it can both transmit genetic information and carry out catalysis as part of ribozymes.[107] This ancient RNA world where nucleic acid would have been used for both catalysis and genetics may have influenced the evolution of the current genetic code based on four nucleotide bases. This would occur since the number of different bases in such an organism is a trade-off between a small number of bases increasing replication accuracy and a large number of bases increasing the catalytic efficiency of ribozymes.[108]

Unfortunately, there is no direct evidence of ancient genetic systems, as recovery of DNA from most fossils is impossible. This is because DNA will survive in the environment for less than one million years and slowly degrades into short fragments in solution.[109] Claims for older DNA have been made, most notably a report of the isolation of a viable bacterium from a salt crystal 250 million years old,[110] but these claims are controversial.[111] [112]

Uses in technology

Genetic engineering

Methods have been developed to purify DNA from organisms, such as phenol-chloroform extraction and manipulate it in the laboratory, such as restriction digests and the polymerase chain reaction. Modern biology and biochemistry make intensive use of these techniques in recombinant DNA technology. Recombinant DNA is a man-made DNA sequence that has been assembled from other DNA sequences. They can be transformed into organisms in the form of plasmids or in the appropriate format, by using a viral vector.[113] The genetically modified organisms produced can be used to produce products such as recombinant proteins, used in medical research,[114] or be grown in agriculture.[115] [116]

Forensics

Forensic scientists can use DNA in blood, semen, skin, saliva or hair found at a crime scene to identify a matching DNA of an individual, such as a perpetrator. This process is called genetic fingerprinting, or more accurately, DNA profiling. In DNA profiling, the lengths of variable sections of repetitive DNA, such as short tandem repeats and minisatellites, are compared between people. This method is usually an extremely reliable technique for identifying a matching DNA.[117] However, identification can be complicated if the scene is contaminated with DNA from several people.[118] DNA profiling was developed in 1984 by British geneticist Sir Alec Jeffreys,[119] and first used in forensic science to convict Colin Pitchfork in the 1988 Enderby murders case.[120]

People convicted of certain types of crimes may be required to provide a sample of DNA for a database. This has helped investigators solve old cases where only a DNA sample was obtained from the scene. DNA profiling can also be used to identify victims of mass casualty incidents.[121] On the other hand, many convicted people have been released from prison on the basis of DNA techniques, which were not available when a crime had originally been committed.

Bioinformatics

Bioinformatics involves the manipulation, searching, and data mining of DNA sequence data. The development of techniques to store and search DNA sequences have led to widely applied advances in computer science, especially string searching algorithms, machine learning and database theory.[122] String searching or matching algorithms, which find an occurrence of a sequence of letters inside a larger sequence of letters, were developed to search for specific sequences of nucleotides.[123] In other applications such as text editors, even simple algorithms for this

problem usually suffice, but DNA sequences cause these algorithms to exhibit near-worst-case behaviour due to their small number of distinct characters. The related problem of sequence alignment aims to identify homologous sequences and locate the specific mutations that make them distinct. These techniques, especially multiple sequence alignment, are used in studying phylogenetic relationships and protein function.[124] Data sets representing entire genomes' worth of DNA sequences, such as those produced by the Human Genome Project, are difficult to use without annotations, which label the locations of genes and regulatory elements on each chromosome. Regions of DNA sequence that have the characteristic patterns associated with protein- or RNA-coding genes can be identified by gene finding algorithms, which allow researchers to predict the presence of particular gene products in an organism even before they have been isolated experimentally.[125]

DNA nanotechnology

DNA nanotechnology uses the unique molecular recognition properties of DNA and other nucleic acids to create self-assembling branched DNA complexes with useful properties.[127] DNA is thus used as a structural material rather than as a carrier of biological information. This has led to the creation of two-dimensional periodic lattices (both tile-based as well as using the "DNA origami" method) as well as three-dimensional structures in the shapes of polyhedra.[128] Nanomechanical devices and algorithmic self-assembly have also been demonstrated,[129] and

The DNA structure at left (schematic shown) will self-assemble into the structure visualized by atomic force microscopy at right. DNA nanotechnology is the field which seeks to design nanoscale structures using the molecular recognition properties of DNA molecules. Image from Strong, 2004.[126]

these DNA structures have been used to template the arrangement of other molecules such as gold nanoparticles and streptavidin proteins.[130]
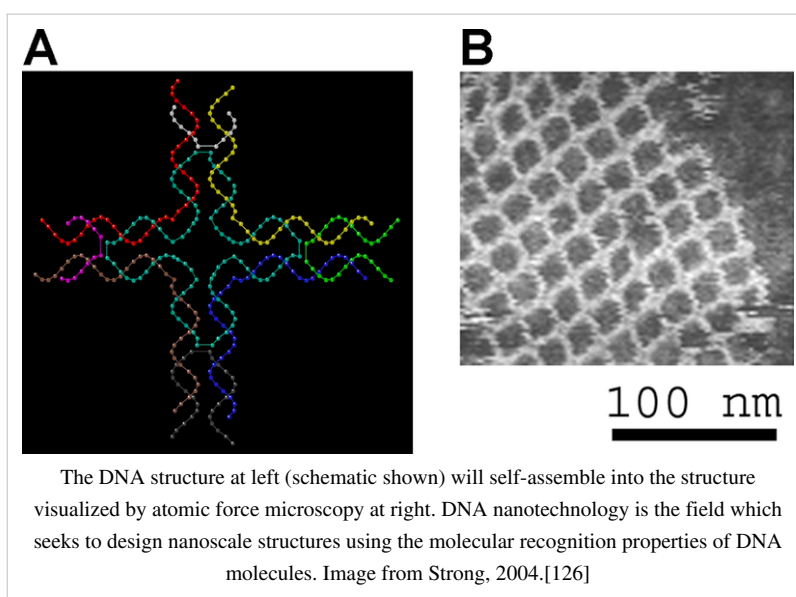
History and anthropology

Because DNA collects mutations over time, which are then inherited, it contains historical information and by comparing DNA sequences, geneticists can infer the evolutionary history of organisms, their phylogeny.[131] This field of phylogenetics is a powerful tool in evolutionary biology. If DNA sequences within a species are compared, population geneticists can learn the history of particular populations. This can be used in studies ranging from ecological genetics to anthropology; for example, DNA evidence is being used to try to identify the Ten Lost Tribes of Israel.[132] [133]

DNA has also been used to look at modern family relationships, such as establishing family relationships between the descendants of Sally Hemings and Thomas Jefferson. This usage is closely related to the use of DNA in criminal investigations detailed above. Indeed, some criminal investigations have been solved when DNA from crime scenes has matched relatives of the guilty individual.[134]

History of DNA research

DNA was first isolated by the Swiss physician Friedrich Miescher who, in 1869, discovered a microscopic substance in the pus of discarded surgical bandages. As it resided in the nuclei of cells, he called it "nuclein".[135] In 1919, Phoebus Levene identified the base, sugar and phosphate nucleotide unit.[136] Levene suggested that DNA consisted of a string of nucleotide units linked together through the phosphate groups. However, Levene thought the chain was short and the bases repeated in a fixed order. In 1937 William Astbury produced the first X-ray diffraction patterns that showed that DNA had a regular structure.[137]

In 1928, Frederick Griffith discovered that traits of the "smooth" form of the *Pneumococcus* could be transferred to the "rough" form of the same bacteria by mixing killed "smooth" bacteria with the live "rough" form.[138] This system provided the first clear suggestion that DNA carried genetic information—the Avery-MacLeod-McCarty experiment—when Oswald Avery, along with coworkers Colin MacLeod and Maclyn McCarty, identified DNA as the transforming principle in 1943.[139] DNA's role in heredity was confirmed in 1952, when Alfred Hershey and Martha Chase in the Hershey-Chase experiment showed that DNA is the genetic material of the T2 phage.[140]
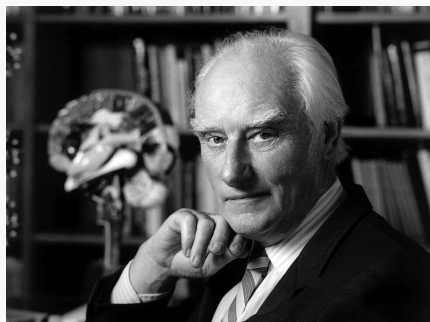
Francis Crick

Rosalind Franklin

Raymond Gosling

In 1953 James D. Watson and Francis Crick suggested what is now accepted as the first correct double-helix model of DNA structure in the journal *Nature*.[9] Their double-helix, molecular model of DNA was then based on a single X-ray diffraction image (labeled as "Photo 51")[141] taken by Rosalind Franklin and Raymond Gosling in May 1952, as well as the information that the DNA bases were paired—also obtained through private communications from Erwin Chargaff in the previous years. Chargaff's rules played a very important role in establishing double-helix configurations for B-DNA as well as A-DNA.

Experimental evidence supporting the Watson and Crick model were published in a series of five articles in the same issue of *Nature*.[142] Of these, Franklin and Gosling's paper was the first publication of their own X-ray diffraction data and original analysis method that partially supported the Watson and Crick model[33] [143] ; this issue also contained an article on DNA structure by Maurice Wilkins and two of his colleagues, whose analysis and *in vivo* B-DNA X-ray patterns also supported the presence *in vivo* of the double-helical DNA configurations as proposed by Crick and Watson for their double-helix molecular model of DNA in the previous two pages of *Nature*.[34] In 1962, after Franklin's death, Watson, Crick, and Wilkins jointly received the Nobel Prize in Physiology or Medicine.[144] Unfortunately, Nobel rules of the time allowed only living recipients, but a vigorous debate continues on who should receive credit for the discovery.[145]

In an influential presentation in 1957, Crick laid out the "Central Dogma" of molecular biology, which foretold the relationship between DNA, RNA, and proteins, and articulated the "adaptor hypothesis".[146] Final confirmation of the replication mechanism that was implied by the double-helical structure followed in 1958 through the Meselson-Stahl experiment.[147] Further work by Crick and coworkers showed that the genetic code was based on non-overlapping triplets of bases, called codons, allowing Har Gobind Khorana, Robert W. Holley and Marshall Warren Nirenberg to decipher the genetic code.[148] These findings represent the birth of molecular biology.

See also

- Crystallography
- DNA microarray
- DNA sequencing
- Genetic disorder
- Junk DNA
- Molecular models of DNA
- Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid
- Nucleic acid analogues
- Nucleic acid methods
- Nucleic acid modeling
- Nucleic Acid Notations
- Paracrystal model and theory
- X-ray crystallography
- X-ray scattering
- Phosphoramidite
- Plasmid
- Polymerase chain reaction
- *Proteopedia DNA* [149]
- Southern blot
- Triple-stranded DNA

Further reading

- Calladine, Chris R.; Drew, Horace R.; Luisi, Ben F. and Travers, Andrew A. (2003). *Understanding DNA: the molecule & how it works*. Amsterdam: Elsevier Academic Press. ISBN 0-12-155089-3.
- Dennis, Carina; Julie Clayton (2003). *50 years of DNA*. Basingstoke: Palgrave Macmillan. ISBN 1-4039-1479-6.
- Judson, Horace Freeland (1996). *The eighth day of creation: makers of the revolution in biology*. Plainview, N.Y: CSHL Press. ISBN 0-87969-478-5.
- Olby, Robert C. (1994). *The path to the double helix: the discovery of DNA*. New York: Dover Publications. ISBN 0-486-68117-3., first published in October 1974 by MacMillan, with foreword by Francis Crick;the definitive DNA textbook,revised in 1994 with a 9 page postscript.
- Olby, Robert C. (2009). *Francis Crick: A Biography*. Plainview, N.Y: Cold Spring Harbor Laboratory Press. ISBN 0-87969-798-9.
- Ridley, Matt (2006). *Francis Crick: discoverer of the genetic code*. [Ashland, OH: Eminent Lives, Atlas Books. ISBN 0-06-082333-X.
- Berry, Andrew; Watson, James D. (2003). *DNA: the secret of life*. New York: Alfred A. Knopf. ISBN 0-375-41546-7.
- Stent, Gunther Siegmund; Watson, James D. (1980). *The double helix: a personal account of the discovery of the structure of DNA*. New York: Norton. ISBN 0-393-95075-1.

- Wilkins, Maurice (2003). *The third man of the double helix the autobiography of Maurice Wilkins*. Cambridge, Eng: University Press. ISBN 0-19-860665-6.

External links

- DNA [150] at the Open Directory Project
- DNA binding site prediction on protein [151]
- DNA coiling to form chromosomes [152]
- DNA from the Beginning [153] Another DNA Learning Center site on DNA, genes, and heredity from Mendel to the human genome project.
- DNA Lab, demonstrates how to extract DNA from wheat using readily available equipment and supplies. [154]
- DNA the Double Helix Game [155] From the official Nobel Prize web site
- DNA under electron microscope [156]
- Dolan DNA Learning Center [157]
- Double Helix: 50 years of DNA [158], *Nature*
- Double Helix 1953–2003 [159] National Centre for Biotechnology Education
- Francis Crick and James Watson talking on the BBC in 1962, 1972, and 1974 [85]
- Genetic Education Modules for Teachers [160]—*DNA from the Beginning* Study Guide
- Guide to DNA cloning [161]
- Olby R (January 2003). "Quiet debut for the double helix" [87]. *Nature* **421** (6921): 402–5. doi:10.1038/nature01397 [162]. PMID 12540907 [163].
- PDB Molecule of the Month *pdb23_1* [164]
- Rosalind Franklin's contributions to the study of DNA [165]
- The Register of Francis Crick Personal Papers 1938 - 2007 [74] at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- U.S. National DNA Day [166]—watch videos and participate in real-time chat with top scientists
- "Clue to chemistry of heredity found" [144]. *The New York Times*. Saturday, June 13, 1953. The first American newspaper coverage of the discovery of the DNA structure.
- An Introduction to DNA and Chromosomes [167] from HOPES: Huntington's Disease Outreach Project for Education at Stanford

References

[1] Russell, Peter (2001). *iGenetics*. New York: Benjamin Cummings. ISBN 0-805-34553-1.

[2] http://en.wikipedia.org/w/index.php?title=Wikipedia_talk:WikiProject_Molecular_and_Cellular_Biology&action=edit&section=new

[3] http://en.wikipedia.org/w/index.php?title=Template:MolBioGeneExp&action=edit

[4] Saenger, Wolfram (1984). *Principles of Nucleic Acid Structure*. New York: Springer-Verlag. ISBN 0387907629.

[5] Alberts, Bruce; Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walters (2002). *Molecular Biology of the Cell; Fourth Edition* (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=mboc4.TOC&depth=2). New York and London: Garland Science. ISBN 0-8153-3218-1. OCLC 145080076 48122761 57023651 69932405 (http://worldcat.org/oclc/145080076+48122761+57023651+69932405). .

[6] Butler, John M. (2001). *Forensic DNA Typing*. Elsevier. ISBN 978-0-12-147951-0. OCLC 223032110 45406517 (http://worldcat.org/oclc/223032110+45406517). pp. 14–15.

[7] Mandelkern M, Elias J, Eden D, Crothers D (1981). "The dimensions of DNA in solution". *J Mol Biol* **152** (1): 153–61. doi: 10.1016/0022-2836(81)90099-1 (http://dx.doi.org/10.1016/0022-2836(81)90099-1). PMID 7338906 (http://www.ncbi.nlm.nih.gov/pubmed/7338906).

[8] Gregory S; Barlow, KF; McLay, KE; Kaul, R; Swarbreck, D; Dunham, A; Scott, CE; Howe, KL *et al*. (2006). "The DNA sequence and biological annotation of human chromosome 1". *Nature* **441** (7091): 315–21. doi: 10.1038/nature04727 (http://dx.doi.org/10.1038/nature04727). PMID 16710414 (http://www.ncbi.nlm.nih.gov/pubmed/16710414).

[9] Watson J.D. and Crick F.H.C. (1953). "A Structure for Deoxyribose Nucleic Acid" (http://www.nature.com/nature/dna50/watsoncrick.pdf) (PDF). *Nature* **171** (4356): 737–738. doi: 10.1038/171737a0 (http://dx.doi.org/10.1038/171737a0). PMID 13054692 (http://www.ncbi.nlm.nih.gov/pubmed/13054692). . Retrieved 4 May 2009.

[10] Berg J., Tymoczko J. and Stryer L. (2002) *Biochemistry.* W. H. Freeman and Company ISBN 0-7167-4955-6

[11] Abbreviations and Symbols for Nucleic Acids, Polynucleotides and their Constituents (http://www.chem.qmul.ac.uk/iupac/misc/naabb. html) IUPAC-IUB Commission on Biochemical Nomenclature (CBN), Accessed 03 January 2006

[12] Ghosh A, Bansal M (2003). "A glossary of DNA structures from A to Z". *Acta Crystallogr D Biol Crystallogr* **59** (Pt 4): 620–6. doi: 10.1107/S0907444903003251 (http://dx.doi.org/10.1107/S0907444903003251). PMID 12657780 (http://www.ncbi.nlm.nih.gov/ pubmed/12657780).

[13] Created from PDB 1D65 (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1D65)

[14] Verma S, Eckstein F (1998). "Modified oligonucleotides: synthesis and strategy for users". *Annu. Rev. Biochem.* **67**: 99–134. doi: 10.1146/annurev.biochem.67.1.99 (http://dx.doi.org/10.1146/annurev.biochem.67.1.99). PMID 9759484 (http://www.ncbi.nlm.nih. gov/pubmed/9759484).

[15] Wing R, Drew H, Takano T, Broka C, Tanaka S, Itakura K, Dickerson R (1980). "Crystal structure analysis of a complete turn of B-DNA". *Nature* **287** (5784): 755–8. doi: 10.1038/287755a0 (http://dx.doi.org/10.1038/287755a0). PMID 7432492 (http://www.ncbi.nlm.nih. gov/pubmed/7432492).

[16] Pabo C, Sauer R (1984). "Protein-DNA recognition". *Annu Rev Biochem* **53**: 293–321. doi: 10.1146/annurev.bi.53.070184.001453 (http:// dx.doi.org/10.1146/annurev.bi.53.070184.001453). PMID 6236744 (http://www.ncbi.nlm.nih.gov/pubmed/6236744).

[17] Clausen-Schaumann H, Rief M, Tolksdorf C, Gaub H (2000). "Mechanical stability of single DNA molecules" (http://www. pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1300792). *Biophys J* **78** (4): 1997–2007. doi: 10.1016/S0006-3495(00)76747-6 (http://dx.doi.org/10.1016/S0006-3495(00)76747-6). PMID 10733978 (http://www.ncbi.nlm.nih. gov/pubmed/10733978).

[18] Yakovchuk P, Protozanova E, Frank-Kamenetskii MD (2006). "Base-stacking and base-pairing contributions into thermal stability of the DNA double helix" (http://nar.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=16449200). *Nucleic Acids Res.* **34** (2): 564–74. doi: 10.1093/nar/gkj454 (http://dx.doi.org/10.1093/nar/gkj454). PMID 16449200 (http://www.ncbi.nlm.nih.gov/pubmed/16449200). PMC 1360284 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1360284). .

[19] Chalikian T, Völker J, Plum G, Breslauer K (1999). "A more unified picture for the thermodynamics of nucleic acid duplex melting: a characterization by calorimetric and volumetric techniques" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez& artid=22151). *Proc Natl Acad Sci USA* **96** (14): 7853–8. doi: 10.1073/pnas.96.14.7853 (http://dx.doi.org/10.1073/pnas.96.14.7853). PMID 10393911 (http://www.ncbi.nlm.nih.gov/pubmed/10393911).

[20] deHaseth P, Helmann J (1995). "Open complex formation by Escherichia coli RNA polymerase: the mechanism of polymerase-induced strand separation of double helical DNA". *Mol Microbiol* **16** (5): 817–24. doi: 10.1111/j.1365-2958.1995.tb02309.x (http://dx.doi.org/10. 1111/j.1365-2958.1995.tb02309.x). PMID 7476180 (http://www.ncbi.nlm.nih.gov/pubmed/7476180).

[21] Isaksson J, Acharya S, Barman J, Cheruku P, Chattopadhyaya J (2004). "Single-stranded adenine-rich DNA and RNA retain structural characteristics of their respective double-stranded conformations and show directional differences in stacking pattern". *Biochemistry* **43** (51): 15996–6010. doi: 10.1021/bi048221v (http://dx.doi.org/10.1021/bi048221v). PMID 15609994 (http://www.ncbi.nlm.nih.gov/ pubmed/15609994).

[22] Designation of the two strands of DNA (http://www.chem.qmul.ac.uk/iubmb/newsletter/misc/DNA.html) JCBN/NC-IUB Newsletter 1989, Accessed 07 May 2008

[23] Hüttenhofer A, Schattner P, Polacek N (2005). "Non-coding RNAs: hope or hype?". *Trends Genet* **21** (5): 289–97. doi: 10.1016/j.tig.2005.03.007 (http://dx.doi.org/10.1016/j.tig.2005.03.007). PMID 15851066 (http://www.ncbi.nlm.nih.gov/pubmed/ 15851066).

[24] Munroe S (2004). "Diversity of antisense regulation in eukaryotes: multiple mechanisms, emerging patterns". *J Cell Biochem* **93** (4): 664–71. doi: 10.1002/jcb.20252 (http://dx.doi.org/10.1002/jcb.20252). PMID 15389973 (http://www.ncbi.nlm.nih.gov/pubmed/ 15389973).

[25] Makalowska I, Lin C, Makalowski W (2005). "Overlapping genes in vertebrate genomes". *Comput Biol Chem* **29** (1): 1–12. doi: 10.1016/j.compbiolchem.2004.12.006 (http://dx.doi.org/10.1016/j.compbiolchem.2004.12.006). PMID 15680581 (http://www.ncbi. nlm.nih.gov/pubmed/15680581).

[26] Johnson Z, Chisholm S (2004). "Properties of overlapping genes are conserved across microbial genomes" (http://www.pubmedcentral. nih.gov/articlerender.fcgi?tool=pmcentrez&artid=525685). *Genome Res* **14** (11): 2268–72. doi: 10.1101/gr.2433104 (http://dx.doi.org/ 10.1101/gr.2433104). PMID 15520290 (http://www.ncbi.nlm.nih.gov/pubmed/15520290).

[27] Lamb R, Horvath C (1991). "Diversity of coding strategies in influenza viruses". *Trends Genet* **7** (8): 261–6. PMID 1771674 (http://www. ncbi.nlm.nih.gov/pubmed/1771674).

[28] Benham C, Mielke S (2005). "DNA mechanics". *Annu Rev Biomed Eng* **7**: 21–53. doi: 10.1146/annurev.bioeng.6.062403.132016 (http:// dx.doi.org/10.1146/annurev.bioeng.6.062403.132016). PMID 16004565 (http://www.ncbi.nlm.nih.gov/pubmed/16004565).

[29] Champoux J (2001). "DNA topoisomerases: structure, function, and mechanism". *Annu Rev Biochem* **70**: 369–413. doi: 10.1146/annurev.biochem.70.1.369 (http://dx.doi.org/10.1146/annurev.biochem.70.1.369). PMID 11395412 (http://www.ncbi.nlm. nih.gov/pubmed/11395412).

[30] Wang J (2002). "Cellular roles of DNA topoisomerases: a molecular perspective". *Nat Rev Mol Cell Biol* **3** (6): 430–40. doi: 10.1038/nrm831 (http://dx.doi.org/10.1038/nrm831). PMID 12042765 (http://www.ncbi.nlm.nih.gov/pubmed/12042765).

[31] Basu H, Feuerstein B, Zarling D, Shafer R, Marton L (1988). "Recognition of Z-RNA and Z-DNA determinants by polyamines in solution: experimental and theoretical studies". *J Biomol Struct Dyn* **6** (2): 299–309. PMID 2482766 (http://www.ncbi.nlm.nih.gov/pubmed/

2482766).

[32] Franklin RE, Gosling RG (6 March 1953). "The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content" (http://hekto.med.unc.edu:8080/CARTER/carter_WWW/Bioch_134/PDF_files/Franklin_Gossling.pdf). *Acta Cryst* **6** (8-9): 673−7. doi: 10.1107/S0365110X53001939 (http://dx.doi.org/10.1107/S0365110X53001939). .
Franklin RE, Gosling RG (September 1953). "The structure of sodium thymonucleate fibres. II. The cylindrically symmetrical Patterson function". *Acta Cryst* **6** (8-9): 678−85. doi: 10.1107/S0365110X53001940 (http://dx.doi.org/10.1107/S0365110X53001940).

[33] Franklin, Rosalind and Gosling, Raymond (1953). "Molecular Configuration in Sodium Thymonucleate. Franklin R. and Gosling R.G" (http://www.nature.com/nature/dna50/franklingosling.pdf) (PDF). *Nature* **171** (4356): 740−1. doi: 10.1038/171740a0 (http://dx.doi.org/10.1038/171740a0). PMID 13054694 (http://www.ncbi.nlm.nih.gov/pubmed/13054694). .

[34] Wilkins M.H.F., A.R. Stokes A.R. & Wilson, H.R. (1953). "Molecular Structure of Deoxypentose Nucleic Acids" (http://www.nature.com/nature/dna50/wilkins.pdf) (PDF). *Nature* **171** (4356): 738−740. doi: 10.1038/171738a0 (http://dx.doi.org/10.1038/171738a0). PMID 13054693 (http://www.ncbi.nlm.nih.gov/pubmed/13054693). .

[35] Leslie AG, Arnott S, Chandrasekaran R, Ratliff RL (1980). "Polymorphism of DNA double helices". *J. Mol. Biol.* **143** (1): 49−72. doi: 10.1016/0022-2836(80)90124-2 (http://dx.doi.org/10.1016/0022-2836(80)90124-2). PMID 7441761 (http://www.ncbi.nlm.nih.gov/pubmed/7441761).

[36] Baianu, I.C. (1980). "Structural Order and Partial Disorder in Biological systems". *Bull. Math. Biol.* **42** (4): 137−141. http://cogprints.org/3822/

[37] Hosemann R., Bagchi R.N., *Direct analysis of diffraction by matter*, North-Holland Publs., Amsterdam − New York, 1962.

[38] Baianu, I.C. (1978). "X-ray scattering by partially disordered membrane systems.". *Acta Cryst.,* **A34** (5): 751−753. doi: 10.1107/S0567739478001540 (http://dx.doi.org/10.1107/S0567739478001540).

[39] Wahl M, Sundaralingam M (1997). "Crystal structures of A-DNA duplexes". *Biopolymers* **44** (1): 45−63. doi:10.1002/(SICI)1097-0282(1997)44:1 (inactive 2009-03-14) . PMID 9097733 (http://www.ncbi.nlm.nih.gov/pubmed/9097733).

[40] Lu XJ, Shakked Z, Olson WK (2000). "A-form conformational motifs in ligand-bound DNA structures". *J. Mol. Biol.* **300** (4): 819−40. doi: 10.1006/jmbi.2000.3690 (http://dx.doi.org/10.1006/jmbi.2000.3690). PMID 10891271 (http://www.ncbi.nlm.nih.gov/pubmed/10891271).

[41] Rothenburg S, Koch-Nolte F, Haag F (2001). "DNA methylation and Z-DNA formation as mediators of quantitative differences in the expression of alleles". *Immunol Rev* **184**: 286−98. doi: 10.1034/j.1600-065x.2001.1840125.x (http://dx.doi.org/10.1034/j.1600-065x.2001.1840125.x). PMID 12086319 (http://www.ncbi.nlm.nih.gov/pubmed/12086319).

[42] Oh D, Kim Y, Rich A (2002). "Z-DNA-binding proteins can act as potent effectors of gene expression in vivo" (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=12486233). *Proc. Natl. Acad. Sci. U.S.A* **99** (26): 16666−71. doi: 10.1073/pnas.262672699 (http://dx.doi.org/10.1073/pnas.262672699). PMID 12486233 (http://www.ncbi.nlm.nih.gov/pubmed/12486233). PMC 139201 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=139201). .

[43] Created from NDB UD0017 (http://ndbserver.rutgers.edu/atlas/xray/structures/U/ud0017/ud0017.html)

[44] Greider C, Blackburn E (1985). "Identification of a specific telomere terminal transferase activity in Tetrahymena extracts". *Cell* **43** (2 Pt 1): 405−13. doi: 10.1016/0092-8674(85)90170-9 (http://dx.doi.org/10.1016/0092-8674(85)90170-9). PMID 3907856 (http://www.ncbi.nlm.nih.gov/pubmed/3907856).

[45] Nugent C, Lundblad V (1998). "The telomerase reverse transcriptase: components and regulation" (http://www.genesdev.org/cgi/content/full/12/8/1073). *Genes Dev* **12** (8): 1073−85. doi: 10.1101/gad.12.8.1073 (http://dx.doi.org/10.1101/gad.12.8.1073). PMID 9553037 (http://www.ncbi.nlm.nih.gov/pubmed/9553037). .

[46] Wright W, Tesmer V, Huffman K, Levene S, Shay J (1997). "Normal human chromosomes have long G-rich telomeric overhangs at one end" (http://www.genesdev.org/cgi/content/full/11/21/2801). *Genes Dev* **11** (21): 2801−9. doi: 10.1101/gad.11.21.2801 (http://dx.doi.org/10.1101/gad.11.21.2801). PMID 9353250 (http://www.ncbi.nlm.nih.gov/pubmed/9353250). PMC 316649 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=316649). .

[47] Burge S, Parkinson G, Hazel P, Todd A, Neidle S (2006). "Quadruplex DNA: sequence, topology and structure" (http://nar.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=17012276). *Nucleic Acids Res* **34** (19): 5402−15. doi: 10.1093/nar/gkl655 (http://dx.doi.org/10.1093/nar/gkl655). PMID 17012276 (http://www.ncbi.nlm.nih.gov/pubmed/17012276). PMC 1636468 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1636468). .

[48] Parkinson G, Lee M, Neidle S (2002). "Crystal structure of parallel quadruplexes from human telomeric DNA". *Nature* **417** (6891): 876−80. doi: 10.1038/nature755 (http://dx.doi.org/10.1038/nature755). PMID 12050675 (http://www.ncbi.nlm.nih.gov/pubmed/12050675).

[49] Griffith J, Comeau L, Rosenfield S, Stansel R, Bianchi A, Moss H, de Lange T (1999). "Mammalian telomeres end in a large duplex loop". *Cell* **97** (4): 503−14. doi: 10.1016/S0092-8674(00)80760-6 (http://dx.doi.org/10.1016/S0092-8674(00)80760-6). PMID 10338214 (http://www.ncbi.nlm.nih.gov/pubmed/10338214).

[50] Seeman NC (November 2005). "DNA enables nanoscale control of the structure of matter". *Q. Rev. Biophys.* **38** (4): 363−71. doi: 10.1017/S0033583505004087 (http://dx.doi.org/10.1017/S0033583505004087). PMID 16515737 (http://www.ncbi.nlm.nih.gov/pubmed/16515737).

[51] Klose R, Bird A (2006). "Genomic DNA methylation: the mark and its mediators". *Trends Biochem Sci* **31** (2): 89−97. doi: 10.1016/j.tibs.2005.12.008 (http://dx.doi.org/10.1016/j.tibs.2005.12.008). PMID 16403636 (http://www.ncbi.nlm.nih.gov/pubmed/16403636).

[52] Bird A (2002). "DNA methylation patterns and epigenetic memory". *Genes Dev* **16** (1): 6–21. doi: 10.1101/gad.947102 (http://dx.doi.org/ 10.1101/gad.947102). PMID 11782440 (http://www.ncbi.nlm.nih.gov/pubmed/11782440).

[53] Walsh C, Xu G (2006). "Cytosine methylation and DNA repair". *Curr Top Microbiol Immunol* **301**: 283–315. doi: 10.1007/3-540-31390-7_11 (http://dx.doi.org/10.1007/3-540-31390-7_11). PMID 16570853 (http://www.ncbi.nlm.nih.gov/pubmed/ 16570853).

[54] Kriaucionis S, Heintz N (May 2009). "The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain". *Science* **324** (5929): 929–30. doi: 10.1126/science.1169786 (http://dx.doi.org/10.1126/science.1169786). PMID 19372393 (http://www. ncbi.nlm.nih.gov/pubmed/19372393).

[55] Ratel D, Ravanat J, Berger F, Wion D (2006). "N6-methyladenine: the other methylated base of DNA" (http://www.pubmedcentral.nih. gov/articlerender.fcgi?tool=pmcentrez&artid=2754416). *Bioessays* **28** (3): 309–15. doi: 10.1002/bies.20342 (http://dx.doi.org/10.1002/ bies.20342). PMID 16479578 (http://www.ncbi.nlm.nih.gov/pubmed/16479578).

[56] Gommers-Ampt J, Van Leeuwen F, de Beer A, Vliegenthart J, Dizdaroglu M, Kowalak J, Crain P, Borst P (1993). "beta-D-glucosyl-hydroxymethyluracil: a novel modified base present in the DNA of the parasitic protozoan T. brucei". *Cell* **75** (6): 1129–36. doi: 10.1016/0092-8674(93)90322-H (http://dx.doi.org/10.1016/0092-8674(93)90322-H). PMID 8261512 (http://www.ncbi.nlm.nih. gov/pubmed/8261512).

[57] Created from PDB 1JDG (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1JDG)

[58] Douki T, Reynaud-Angelin A, Cadet J, Sage E (2003). "Bipyrimidine photoproducts rather than oxidative lesions are the main type of DNA damage involved in the genotoxic effect of solar UVA radiation". *Biochemistry* **42** (30): 9221–6. doi: 10.1021/bi034593c (http://dx.doi.org/ 10.1021/bi034593c). PMID 12885257 (http://www.ncbi.nlm.nih.gov/pubmed/12885257).,

[59] Cadet J, Delatour T, Douki T, Gasparutto D, Pouget J, Ravanat J, Sauvaigo S (1999). "Hydroxyl radicals and DNA base damage". *Mutat Res* **424** (1–2): 9–21. PMID 10064846 (http://www.ncbi.nlm.nih.gov/pubmed/10064846).

[60] Beckman KB, Ames BN (August 1997). "Oxidative decay of DNA" (http://www.jbc.org/cgi/pmidlookup?view=long&pmid=9289489). *J. Biol. Chem.* **272** (32): 19633–6. doi: 10.1074/jbc.272.32.19633 (http://dx.doi.org/10.1074/jbc.272.32.19633). PMID 9289489 (http:// www.ncbi.nlm.nih.gov/pubmed/9289489). .

[61] Valerie K, Povirk L (2003). "Regulation and mechanisms of mammalian double-strand break repair". *Oncogene* **22** (37): 5792–812. doi: 10.1038/sj.onc.1206679 (http://dx.doi.org/10.1038/sj.onc.1206679). PMID 12947387 (http://www.ncbi.nlm.nih.gov/pubmed/ 12947387).

[62] Ferguson L, Denny W (1991). "The genetic toxicology of acridines". *Mutat Res* **258** (2): 123–60. PMID 1881402 (http://www.ncbi.nlm. nih.gov/pubmed/1881402).

[63] Jeffrey A (1985). "DNA modification by chemical carcinogens". *Pharmacol Ther* **28** (2): 237–72. doi: 10.1016/0163-7258(85)90013-0 (http://dx.doi.org/10.1016/0163-7258(85)90013-0). PMID 3936066 (http://www.ncbi.nlm.nih.gov/pubmed/3936066).

[64] Stephens T, Bunde C, Fillmore B (2000). "Mechanism of action in thalidomide teratogenesis". *Biochem Pharmacol* **59** (12): 1489–99. doi: 10.1016/S0006-2952(99)00388-3 (http://dx.doi.org/10.1016/S0006-2952(99)00388-3). PMID 10799645 (http://www.ncbi.nlm.nih. gov/pubmed/10799645).

[65] Braña M, Cacho M, Gradillas A, de Pascual-Teresa B, Ramos A (2001). "Intercalators as anticancer drugs". *Curr Pharm Des* **7** (17): 1745–80. doi: 10.2174/1381612013397113 (http://dx.doi.org/10.2174/1381612013397113). PMID 11562309 (http://www.ncbi.nlm. nih.gov/pubmed/11562309).

[66] Venter J; Adams, MD; Myers, EW; Li, PW; Mural, RJ; Sutton, GG; Smith, HO; Yandell, M *et al*. (2001). "The sequence of the human genome". *Science* **291** (5507): 1304–51. doi: 10.1126/science.1058040 (http://dx.doi.org/10.1126/science.1058040). PMID 11181995 (http://www.ncbi.nlm.nih.gov/pubmed/11181995).

[67] Thanbichler M, Wang S, Shapiro L (2005). "The bacterial nucleoid: a highly organized and dynamic structure". *J Cell Biochem* **96** (3): 506–21. doi: 10.1002/jcb.20519 (http://dx.doi.org/10.1002/jcb.20519). PMID 15988757 (http://www.ncbi.nlm.nih.gov/pubmed/ 15988757).

[68] Wolfsberg T, McEntyre J, Schuler G (2001). "Guide to the draft human genome". *Nature* **409** (6822): 824–6. doi: 10.1038/35057000 (http:/ /dx.doi.org/10.1038/35057000). PMID 11236998 (http://www.ncbi.nlm.nih.gov/pubmed/11236998).

[69] Gregory T (2005). "The C-value enigma in plants and animals: a review of parallels and an appeal for partnership" (http://aob. oxfordjournals.org/cgi/content/full/95/1/133). *Ann Bot (Lond)* **95** (1): 133–46. doi: 10.1093/aob/mci009 (http://dx.doi.org/10.1093/ aob/mci009). PMID 15596463 (http://www.ncbi.nlm.nih.gov/pubmed/15596463). .

[70] The ENCODE Project Consortium (2007). "Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2212820). *Nature* **447** (7146): 799–816. doi: 10.1038/nature05874 (http://dx.doi.org/10.1038/nature05874). PMID 17571346 (http://www.ncbi.nlm.nih.gov/pubmed/17571346).

[71] Created from PDB 1MSW (http://www.rcsb.org/pdb/explore/explore.do?structureId=1MSW)

[72] Pidoux A, Allshire R (2005). "The role of heterochromatin in centromere function" (http://www.pubmedcentral.nih.gov/articlerender. fcgi?tool=pmcentrez&artid=1569473). *Philos Trans R Soc Lond B Biol Sci* **360** (1455): 569–79. doi: 10.1098/rstb.2004.1611 (http://dx.doi. org/10.1098/rstb.2004.1611). PMID 15905142 (http://www.ncbi.nlm.nih.gov/pubmed/15905142).

[73] Harrison P, Hegyi H, Balasubramanian S, Luscombe N, Bertone P, Echols N, Johnson T, Gerstein M (2002). "Molecular fossils in the human genome: identification and analysis of the pseudogenes in chromosomes 21 and 22" (http://www.genome.org/cgi/content/full/12/ 2/272). *Genome Res* **12** (2): 272–80. doi: 10.1101/gr.207102 (http://dx.doi.org/10.1101/gr.207102). PMID 11827946 (http://www.ncbi. nlm.nih.gov/pubmed/11827946). PMC 155275 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=155275).

.

[74] Harrison P, Gerstein M (2002). "Studying genomes through the aeons: protein families, pseudogenes and proteome evolution". *J Mol Biol* **318** (5): 1155−74. doi: 10.1016/S0022-2836(02)00109-2 (http://dx.doi.org/10.1016/S0022-2836(02)00109-2). PMID 12083509 (http://www.ncbi.nlm.nih.gov/pubmed/12083509).

[75] Albà M (2001). "Replicative DNA polymerases" (http://genomebiology.com/1465-6906/2/REVIEWS3002). *Genome Biol* **2** (1): REVIEWS3002. doi: 10.1186/gb-2001-2-1-reviews3002 (http://dx.doi.org/10.1186/gb-2001-2-1-reviews3002). PMID 11178285 (http://www.ncbi.nlm.nih.gov/pubmed/11178285). PMC 150442 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=150442). .

[76] Sandman K, Pereira S, Reeve J (1998). "Diversity of prokaryotic chromosomal proteins and the origin of the nucleosome". *Cell Mol Life Sci* **54** (12): 1350−64. doi: 10.1007/s000180050259 (http://dx.doi.org/10.1007/s000180050259). PMID 9893710 (http://www.ncbi.nlm.nih.gov/pubmed/9893710).

[77] Dame RT (2005). "The role of nucleoid-associated proteins in the organization and compaction of bacterial chromatin". *Mol. Microbiol.* **56** (4): 858−70. doi: 10.1111/j.1365-2958.2005.04598.x (http://dx.doi.org/10.1111/j.1365-2958.2005.04598.x). PMID 15853876 (http://www.ncbi.nlm.nih.gov/pubmed/15853876).

[78] Luger K, Mäder A, Richmond R, Sargent D, Richmond T (1997). "Crystal structure of the nucleosome core particle at 2.8 A resolution". *Nature* **389** (6648): 251−60. doi: 10.1038/38444 (http://dx.doi.org/10.1038/38444). PMID 9305837 (http://www.ncbi.nlm.nih.gov/pubmed/9305837).

[79] Jenuwein T, Allis C (2001). "Translating the histone code". *Science* **293** (5532): 1074−80. doi: 10.1126/science.1063127 (http://dx.doi.org/10.1126/science.1063127). PMID 11498575 (http://www.ncbi.nlm.nih.gov/pubmed/11498575).

[80] Ito T (2003). "Nucleosome assembly and remodelling". *Curr Top Microbiol Immunol* **274**: 1−22. PMID 12596902 (http://www.ncbi.nlm.nih.gov/pubmed/12596902).

[81] Thomas J (2001). "HMG1 and 2: architectural DNA-binding proteins". *Biochem Soc Trans* **29** (Pt 4): 395−401. doi: 10.1042/BST0290395 (http://dx.doi.org/10.1042/BST0290395). PMID 11497996 (http://www.ncbi.nlm.nih.gov/pubmed/11497996).

[82] Grosschedl R, Giese K, Pagel J (1994). "HMG domain proteins: architectural elements in the assembly of nucleoprotein structures". *Trends Genet* **10** (3): 94−100. doi: 10.1016/0168-9525(94)90232-1 (http://dx.doi.org/10.1016/0168-9525(94)90232-1). PMID 8178371 (http://www.ncbi.nlm.nih.gov/pubmed/8178371).

[83] Iftode C, Daniely Y, Borowiec J (1999). "Replication protein A (RPA): the eukaryotic SSB". *Crit Rev Biochem Mol Biol* **34** (3): 141−80. doi: 10.1080/10409239991209255 (http://dx.doi.org/10.1080/10409239991209255). PMID 10473346 (http://www.ncbi.nlm.nih.gov/pubmed/10473346).

[84] Created from PDB 1LMB (http://www.rcsb.org/pdb/explore/explore.do?structureId=1LMB)

[85] Myers L, Kornberg R (2000). "Mediator of transcriptional regulation". *Annu Rev Biochem* **69**: 729−49. doi: 10.1146/annurev.biochem.69.1.729 (http://dx.doi.org/10.1146/annurev.biochem.69.1.729). PMID 10966474 (http://www.ncbi.nlm.nih.gov/pubmed/10966474).

[86] Spiegelman B, Heinrich R (2004). "Biological control through regulated transcriptional coactivators". *Cell* **119** (2): 157−67. doi: 10.1016/j.cell.2004.09.037 (http://dx.doi.org/10.1016/j.cell.2004.09.037). PMID 15479634 (http://www.ncbi.nlm.nih.gov/pubmed/15479634).

[87] Li Z, Van Calcar S, Qu C, Cavenee W, Zhang M, Ren B (2003). "A global transcriptional regulatory role for c-Myc in Burkitt's lymphoma cells" (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=12808131). *Proc Natl Acad Sci USA* **100** (14): 8164−9. doi: 10.1073/pnas.1332764100 (http://dx.doi.org/10.1073/pnas.1332764100). PMID 12808131 (http://www.ncbi.nlm.nih.gov/pubmed/12808131). PMC 166200 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=166200). .

[88] Pabo C, Sauer R (1984). "Protein-DNA recognition". *Annu Rev Biochem* **53**: 293−321. doi: 10.1146/annurev.bi.53.070184.001453 (http://dx.doi.org/10.1146/annurev.bi.53.070184.001453). PMID 6236744 (http://www.ncbi.nlm.nih.gov/pubmed/6236744).

[89] Created from PDB 1RVA (http://www.rcsb.org/pdb/explore/explore.do?structureId=1RVA)

[90] Bickle T, Krüger D (1993). "Biology of DNA restriction" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=372918). *Microbiol Rev* **57** (2): 434−50. PMID 8336674 (http://www.ncbi.nlm.nih.gov/pubmed/8336674).

[91] Doherty A, Suh S (2000). "Structural and mechanistic conservation in DNA ligases" (http://nar.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=11058099). *Nucleic Acids Res* **28** (21): 4051−8. doi: 10.1093/nar/28.21.4051 (http://dx.doi.org/10.1093/nar/28.21.4051). PMID 11058099 (http://www.ncbi.nlm.nih.gov/pubmed/11058099). PMC 113121 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=113121). .

[92] Schoeffler A, Berger J (2005). "Recent advances in understanding structure-function relationships in the type II topoisomerase mechanism". *Biochem Soc Trans* **33** (Pt 6): 1465−70. doi: 10.1042/BST20051465 (http://dx.doi.org/10.1042/BST20051465). PMID 16246147 (http://www.ncbi.nlm.nih.gov/pubmed/16246147).

[93] Tuteja N, Tuteja R (2004). "Unraveling DNA helicases. Motif, structure, mechanism and function". *Eur J Biochem* **271** (10): 1849−63. doi: 10.1111/j.1432-1033.2004.04094.x (http://dx.doi.org/10.1111/j.1432-1033.2004.04094.x). PMID 15128295 (http://www.ncbi.nlm.nih.gov/pubmed/15128295).

[94] Joyce C, Steitz T (1995). "Polymerase structures and function: variations on a theme?" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=177480). *J Bacteriol* **177** (22): 6321−9. PMID 7592405 (http://www.ncbi.nlm.nih.gov/pubmed/7592405).

[95] Hubscher U, Maga G, Spadari S (2002). "Eukaryotic DNA polymerases". *Annu Rev Biochem* **71**: 133−63. doi: 10.1146/annurev.biochem.71.090501.150041 (http://dx.doi.org/10.1146/annurev.biochem.71.090501.150041). PMID 12045093 (http:/

/www.ncbi.nlm.nih.gov/pubmed/12045093).

[96] Johnson A, O'Donnell M (2005). "Cellular DNA replicases: components and dynamics at the replication fork". *Annu Rev Biochem* **74**: 283–315. doi: 10.1146/annurev.biochem.73.011303.073859 (http://dx.doi.org/10.1146/annurev.biochem.73.011303.073859). PMID 15952889 (http://www.ncbi.nlm.nih.gov/pubmed/15952889).

[97] Tarrago-Litvak L, Andréola M, Nevinsky G, Sarih-Cottin L, Litvak S (1 May 1994). "The reverse transcriptase of HIV-1: from enzymology to therapeutic intervention" (http://www.fasebj.org/cgi/reprint/8/8/497). *FASEB J* **8** (8): 497–503. PMID 7514143 (http://www.ncbi.nlm.nih.gov/pubmed/7514143). .

[98] Martinez E (2002). "Multi-protein complexes in eukaryotic gene transcription". *Plant Mol Biol* **50** (6): 925–47. doi: 10.1023/A:1021258713850 (http://dx.doi.org/10.1023/A:1021258713850). PMID 12516863 (http://www.ncbi.nlm.nih.gov/pubmed/12516863).

[99] Created from PDB 1M6G (http://www.rcsb.org/pdb/explore/explore.do?structureId=1M6G)

[100] Cremer T, Cremer C (2001). "Chromosome territories, nuclear architecture and gene regulation in mammalian cells". *Nat Rev Genet* **2** (4): 292–301. doi: 10.1038/35066075 (http://dx.doi.org/10.1038/35066075). PMID 11283701 (http://www.ncbi.nlm.nih.gov/pubmed/11283701).

[101] Pál C, Papp B, Lercher M (2006). "An integrated view of protein evolution". *Nat Rev Genet* **7** (5): 337–48. doi: 10.1038/nrg1838 (http://dx.doi.org/10.1038/nrg1838). PMID 16619049 (http://www.ncbi.nlm.nih.gov/pubmed/16619049).

[102] O'Driscoll M, Jeggo P (2006). "The role of double-strand break repair - insights from human genetics". *Nat Rev Genet* **7** (1): 45–54. doi: 10.1038/nrg1746 (http://dx.doi.org/10.1038/nrg1746). PMID 16369571 (http://www.ncbi.nlm.nih.gov/pubmed/16369571).

[103] Vispé S, Defais M (1997). "Mammalian Rad51 protein: a RecA homologue with pleiotropic functions". *Biochimie* **79** (9-10): 587–92. doi: 10.1016/S0300-9084(97)82007-X (http://dx.doi.org/10.1016/S0300-9084(97)82007-X). PMID 9466696 (http://www.ncbi.nlm.nih.gov/pubmed/9466696).

[104] Neale MJ, Keeney S (2006). "Clarifying the mechanics of DNA strand exchange in meiotic recombination". *Nature* **442** (7099): 153–8. doi: 10.1038/nature04885 (http://dx.doi.org/10.1038/nature04885). PMID 16838012 (http://www.ncbi.nlm.nih.gov/pubmed/16838012).

[105] Dickman M, Ingleston S, Sedelnikova S, Rafferty J, Lloyd R, Grasby J, Hornby D (2002). "The RuvABC resolvasome". *Eur J Biochem* **269** (22): 5492–501. doi: 10.1046/j.1432-1033.2002.03250.x (http://dx.doi.org/10.1046/j.1432-1033.2002.03250.x). PMID 12423347 (http://www.ncbi.nlm.nih.gov/pubmed/12423347).

[106] Orgel L (2004). "Prebiotic chemistry and the origin of the RNA world" (http://www.crbmb.com/cgi/reprint/39/2/99.pdf) (PDF). *Crit Rev Biochem Mol Biol* **39** (2): 99–123. doi: 10.1080/10409230490460765 (http://dx.doi.org/10.1080/10409230490460765). PMID 15217990 (http://www.ncbi.nlm.nih.gov/pubmed/15217990). .

[107] Davenport R (2001). "Ribozymes. Making copies in the RNA world". *Science* **292** (5520): 1278. doi: 10.1126/science.292.5520.1278a (http://dx.doi.org/10.1126/science.292.5520.1278a). PMID 11360970 (http://www.ncbi.nlm.nih.gov/pubmed/11360970).

[108] Szathmáry E (1992). "What is the optimum size for the genetic alphabet?" (http://www.pnas.org/cgi/reprint/89/7/2614.pdf) (PDF). *Proc Natl Acad Sci USA* **89** (7): 2614–8. doi: 10.1073/pnas.89.7.2614 (http://dx.doi.org/10.1073/pnas.89.7.2614). PMID 1372984 (http://www.ncbi.nlm.nih.gov/pubmed/1372984). PMC 48712 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=48712). .

[109] Lindahl T (1993). "Instability and decay of the primary structure of DNA". *Nature* **362** (6422): 709–15. doi: 10.1038/362709a0 (http://dx.doi.org/10.1038/362709a0). PMID 8469282 (http://www.ncbi.nlm.nih.gov/pubmed/8469282).

[110] Vreeland R, Rosenzweig W, Powers D (2000). "Isolation of a 250 million-year-old halotolerant bacterium from a primary salt crystal". *Nature* **407** (6806): 897–900. doi: 10.1038/35038060 (http://dx.doi.org/10.1038/35038060). PMID 11057666 (http://www.ncbi.nlm.nih.gov/pubmed/11057666).

[111] Hebsgaard M, Phillips M, Willerslev E (2005). "Geologically ancient DNA: fact or artefact?". *Trends Microbiol* **13** (5): 212–20. doi: 10.1016/j.tim.2005.03.010 (http://dx.doi.org/10.1016/j.tim.2005.03.010). PMID 15866038 (http://www.ncbi.nlm.nih.gov/pubmed/15866038).

[112] Nickle D, Learn G, Rain M, Mullins J, Mittler J (2002). "Curiously modern DNA for a "250 million-year-old" bacterium". *J Mol Evol* **54** (1): 134–7. doi: 10.1007/s00239-001-0025-x (http://dx.doi.org/10.1007/s00239-001-0025-x). PMID 11734907 (http://www.ncbi.nlm.nih.gov/pubmed/11734907).

[113] Goff SP, Berg P (1976). "Construction of hybrid viruses containing SV40 and lambda phage DNA segments and their propagation in cultured monkey cells". *Cell* **9** (4 PT 2): 695–705. doi: 10.1016/0092-8674(76)90133-1 (http://dx.doi.org/10.1016/0092-8674(76)90133-1). PMID 189942 (http://www.ncbi.nlm.nih.gov/pubmed/189942).

[114] Houdebine L (2007). "Transgenic animal models in biomedical research". *Methods Mol Biol* **360**: 163–202. doi: 10.1385/1-59745-165-7:163 (http://dx.doi.org/10.1385/1-59745-165-7:163). PMID 17172731 (http://www.ncbi.nlm.nih.gov/pubmed/17172731).

[115] Daniell H, Dhingra A (2002). "Multigene engineering: dawn of an exciting new era in biotechnology". *Curr Opin Biotechnol* **13** (2): 136–41. doi: 10.1016/S0958-1669(02)00297-5 (http://dx.doi.org/10.1016/S0958-1669(02)00297-5). PMID 11950565 (http://www.ncbi.nlm.nih.gov/pubmed/11950565).

[116] Job D (2002). "Plant biotechnology in agriculture". *Biochimie* **84** (11): 1105–10. doi: 10.1016/S0300-9084(02)00013-5 (http://dx.doi.org/10.1016/S0300-9084(02)00013-5). PMID 12595138 (http://www.ncbi.nlm.nih.gov/pubmed/12595138).

[117] Collins A, Morton N (1994). "Likelihood ratios for DNA identification" (http://www.pnas.org/cgi/reprint/91/13/6007.pdf) (PDF). *Proc Natl Acad Sci USA* **91** (13): 6007–11. doi: 10.1073/pnas.91.13.6007 (http://dx.doi.org/10.1073/pnas.91.13.6007). PMID 8016106 (http://www.ncbi.nlm.nih.gov/pubmed/8016106). PMC 44126 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=44126). .

[118] Weir B, Triggs C, Starling L, Stowell L, Walsh K, Buckleton J (1997). "Interpreting DNA mixtures". *J Forensic Sci* **42** (2): 213–22. PMID 9068179 (http://www.ncbi.nlm.nih.gov/pubmed/9068179).

[119] Jeffreys A, Wilson V, Thein S (1985). "Individual-specific 'fingerprints' of human DNA". *Nature* **316** (6023): 76–9. doi: 10.1038/316076a0 (http://dx.doi.org/10.1038/316076a0). PMID 2989708 (http://www.ncbi.nlm.nih.gov/pubmed/2989708).

[120] Colin Pitchfork — first murder conviction on DNA evidence also clears the prime suspect (http://www.forensic.gov.uk/forensic_t/inside/news/list_casefiles.php?case=1) Forensic Science Service Accessed 23 December 2006

[121] "DNA Identification in Mass Fatality Incidents" (http://massfatality.dna.gov/Introduction/). National Institute of Justice. September 2006. .

[122] Baldi, Pierre; Brunak, Soren (2001). *Bioinformatics: The Machine Learning Approach*. MIT Press. ISBN 978-0-262-02506-5. OCLC 45951728 (http://worldcat.org/oclc/45951728)..

[123] Gusfield, Dan. *Algorithms on Strings, Trees, and Sequences: Computer Science and Computational Biology*. Cambridge University Press, 15 January 1997. ISBN 978-0-521-58519-4.

[124] Sjölander K (2004). "Phylogenomic inference of protein molecular function: advances and challenges" (http://bioinformatics.oxfordjournals.org/cgi/reprint/20/2/170). *Bioinformatics* **20** (2): 170–9. doi: 10.1093/bioinformatics/bth021 (http://dx.doi.org/10.1093/bioinformatics/bth021). PMID 14734307 (http://www.ncbi.nlm.nih.gov/pubmed/14734307). .

[125] Mount DM (2004). *Bioinformatics: Sequence and Genome Analysis* (2 ed.). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press. ISBN 0879697121. OCLC 55106399 (http://worldcat.org/oclc/55106399).

[126] http://dx.doi.org/10.1371/journal.pbio.0020073

[127] Rothemund PW (March 2006). "Folding DNA to create nanoscale shapes and patterns". *Nature* **440** (7082): 297–302. doi: 10.1038/nature04586 (http://dx.doi.org/10.1038/nature04586). PMID 16541064 (http://www.ncbi.nlm.nih.gov/pubmed/16541064).

[128] Andersen ES, Dong M, Nielsen MM (May 2009). "Self-assembly of a nanoscale DNA box with a controllable lid". *Nature* **459** (7243): 73–6. doi: 10.1038/nature07971 (http://dx.doi.org/10.1038/nature07971). PMID 19424153 (http://www.ncbi.nlm.nih.gov/pubmed/19424153).

[129] Ishitsuka Y, Ha T (May 2009). "DNA nanotechnology: a nanomachine goes live". *Nat Nanotechnol* **4** (5): 281–2. doi: 10.1038/nnano.2009.101 (http://dx.doi.org/10.1038/nnano.2009.101). PMID 19421208 (http://www.ncbi.nlm.nih.gov/pubmed/19421208).

[130] Aldaye FA, Palmer AL, Sleiman HF (September 2008). "Assembling materials with DNA as the guide". *Science* **321** (5897): 1795–9. doi: 10.1126/science.1154533 (http://dx.doi.org/10.1126/science.1154533). PMID 18818351 (http://www.ncbi.nlm.nih.gov/pubmed/18818351).

[131] Wray G; Martindale, Mark Q. (2002). "Dating branches on the tree of life using DNA" (http://genomebiology.com/1465-6906/3/REVIEWS0001). *Genome Biol* **3** (1): REVIEWS0001. doi: 10.1046/j.1525-142X.1999.99010.x (http://dx.doi.org/10.1046/j.1525-142X.1999.99010.x). PMID 11806830 (http://www.ncbi.nlm.nih.gov/pubmed/11806830). PMC 150454 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=150454). .

[132] *Lost Tribes of Israel*, NOVA, PBS airdate: 22 February 2000. Transcript available from PBS.org, (http://www.pbs.org/wgbh/nova/transcripts/2706israel.html) (last accessed on 4 March 2006)

[133] Kleiman, Yaakov. "The Cohanim/DNA Connection: The fascinating story of how DNA studies confirm an ancient biblical tradition". (http://www.aish.com/societywork/sciencenature/the_cohanim_-_dna_connection.asp) *aish.com* (January 13, 2000). Accessed 4 March 2006.

[134] Bhattacharya, Shaoni. "Killer convicted thanks to relative's DNA". (http://www.newscientist.com/article.ns?id=dn4908) *newscientist.com* (20 April 2004). Accessed 22 December 06

[135] Dahm R (January 2008). "Discovering DNA: Friedrich Miescher and the early years of nucleic acid research". *Hum. Genet.* **122** (6): 565–81. doi: 10.1007/s00439-007-0433-0 (http://dx.doi.org/10.1007/s00439-007-0433-0). PMID 17901982 (http://www.ncbi.nlm.nih.gov/pubmed/17901982).

[136] Levene P, (1 December 1919). "The structure of yeast nucleic acid" (http://www.jbc.org/cgi/reprint/40/2/415). *J Biol Chem* **40** (2): 415–24. .

[137] Astbury W, (1947). "Nucleic acid". *Symp. SOC. Exp. Bbl* **1** (66).

[138] Lorenz MG, Wackernagel W (1 September 1994). "Bacterial gene transfer by natural genetic transformation in the environment" (http://mmbr.asm.org/cgi/pmidlookup?view=long&pmid=7968924). *Microbiol. Rev.* **58** (3): 563–602. PMID 7968924 (http://www.ncbi.nlm.nih.gov/pubmed/7968924). PMC 372978 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=372978). .

[139] Avery O, MacLeod C, McCarty M (1944). "Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Inductions of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III" (http://www.jem.org/cgi/reprint/149/2/297). *J Exp Med* **79** (2): 137–158. doi: 10.1084/jem.79.2.137 (http://dx.doi.org/10.1084/jem.79.2.137). PMID 19871359 (http://www.ncbi.nlm.nih.gov/pubmed/19871359). PMC 2135445 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2135445). .

[140] Hershey A, Chase M (1952). "Independent functions of viral protein and nucleic acid in growth of bacteriophage" (http://www.jgp.org/cgi/reprint/36/1/39.pdf) (PDF). *J Gen Physiol* **36** (1): 39−56. doi: 10.1085/jgp.36.1.39 (http://dx.doi.org/10.1085/jgp.36.1.39). PMID 12981234 (http://www.ncbi.nlm.nih.gov/pubmed/12981234). PMC 2147348 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2147348). .

[141] The B-DNA X-ray pattern on the right of this linked image (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/pictures/sci9.001.5.html) was obtained by Rosalind Franklin and Raymond Gosling in May 1952 at high hydration levels of DNA and it has been labeled as "Photo 51"

[142] Nature Archives Double Helix of DNA: 50 Years (http://www.nature.com/nature/dna50/archive.html)

[143] Original X-ray diffraction image (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/pictures/franklin-typeBphoto.html)

[144] The Nobel Prize in Physiology or Medicine 1962 (http://nobelprize.org/nobel_prizes/medicine/laureates/1962/) Nobelprize .org Accessed 22 December 06

[145] Brenda Maddox (23 January 2003). "The double helix and the 'wronged heroine'" (http://www.biomath.nyu.edu/index/course/hw_articles/nature4.pdf) (PDF). *Nature* **421** (6921): 407−408. doi: 10.1038/nature01399 (http://dx.doi.org/10.1038/nature01399). PMID 12540909 (http://www.ncbi.nlm.nih.gov/pubmed/12540909). .

[146] Crick, F.H.C. On degenerate templates and the adaptor hypothesis (PDF). (http://genome.wellcome.ac.uk/assets/wtx030893.pdf) genome.wellcome.ac.uk (Lecture, 1955). Accessed 22 December 2006

[147] Meselson M, Stahl F (1958). "The replication of DNA in *Escherichia coli*" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=528642). *Proc Natl Acad Sci USA* **44** (7): 671−82. doi: 10.1073/pnas.44.7.671 (http://dx.doi.org/10.1073/pnas.44.7.671). PMID 16590258 (http://www.ncbi.nlm.nih.gov/pubmed/16590258).

[148] The Nobel Prize in Physiology or Medicine 1968 (http://nobelprize.org/nobel_prizes/medicine/laureates/1968/) Nobelprize.org Accessed 22 December 06

[149] http://proteopedia.org/wiki/index.php/DNA

[150] http://www.dmoz.org/Science/Biology/Biochemistry_and_Molecular_Biology/Biomolecules/Nucleic_Acids/DNA//

[151] http://pipe.scs.fsu.edu/displar.html

[152] http://biostudio.com/c_%20education%20mac.htm

[153] http://www.dnaftb.org/dnaftb/

[154] http://ca.youtube.com/watch?v=iyb7fwduuGM

[155] http://nobelprize.org/educational_games/medicine/dna_double_helix/

[156] http://www.fidelitysystems.com/Unlinked_DNA.html

[157] http://www.dnalc.org/

[158] http://www.nature.com/nature/dna50/archive.html

[159] http://www.ncbe.reading.ac.uk/DNA50/

[160] http://www.genome.gov/10506718

[161] http://www.blackwellpublishing.com/trun/artwork/Animations/cloningexp/cloningexp.html

[162] http://dx.doi.org/10.1038%2Fnature01397

[163] http://www.ncbi.nlm.nih.gov/pubmed/12540907

[164] http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb23_1.html

[165] http://mason.gmu.edu/~emoody/rfranklin.html

[166] http://www.genome.gov/10506367

[167] http://hopes.stanford.edu/basics/dna/b0.html

Chargaff's rules

Chargaff's rules state that DNA from any cell of all organisms should have a 1:1 ratio of pyrimidine and purine bases and, more specifically, that the amount of guanine is equal to cytosine and the amount of adenine is equal to thymine. This pattern is found in both strands of the DNA. They were discovered by Austrian chemist Erwin Chargaff.[1] [2] [3] [4] [5] [6]

Chargaff Parity Rule 1

The first rule holds that a double-stranded DNA molecule *globally* has percentage base pair equality: %A = %T and %G = %C.[6] The rigorous validation of the rule constitutes the basis of Watson-Crick pairs in the DNA double helix.

Chargaff Parity Rule 2

The second rule holds that both %A ~ %T and %G ~ %C are valid for each of the two DNA strands.[7] This describes only a global feature of the base composition in a single DNA strand.[8]

Research

The second of Chargaff's rules (or "Chargaff's second parity rule") is that the composition of DNA varies from one species to another; in particular in the relative amounts of A, G, T, and C bases. Such evidence of molecular diversity, which had been presumed absent from DNA, made DNA a more credible candidate for the genetic material than protein.

In 2006 it was shown that this rule applies to four of the five types of double stranded genomes; specifically it applies to the eukaryotic chromosomes, the bacterial chromosomes, the double stranded DNA viral genomes, and the archeal chromosomes.[9] It does not apply to the organellar genomes (mitochondria and plastids) nor does it apply to the single stranded DNA (viral) genomes or any type of RNA genome. The basis for this rule is still under investigation.

The rule itself has consequences. In most bacterial genomes (which are generally 80-90% coding) genes are arranged in such a fashion that approximately 50% of the coding sequence lies on either strand. Wacław Szybalski, in the 1960s, showed that in bacteriophage coding sequences purines (A and G) exceed pyrimidines (C and T).[10] This rule has since been confirmed in other organisms and should probably be now termed "Szybalski's rule". While Szybalski's rule generally holds, exceptions are known to exist.[11] [12] [13] The biological basis for Szybalski's rule, like Chargaff's, is not yet known.

The combined effect of Chargaff's second rule and Szybalski's rule can be seen in bacterial genomes where the coding sequences are not equally distributed. The genetic code has 64 codons of which 3 function as termination codons: there are only 20 amino acids normally present in proteins. (There are two uncommon amino acids - selenocysteine and pyrrolysine - found in a limited number of proteins and encoded by the 'stop' codons - TGA and TAG respectively.) The mismatch between the number of codons and amino acids allows several codons to code for a single amino acid. These codons normally differ in the third codon base position.

Multivariate statistical analysis of codon use within genomes with unequal quantities of coding sequences on the two strands has shown that codon use in the third position depends on the strand on which the gene is located. This seems likely to be the result of Szybalski's and Chargaff's rules. Because of the asymmetry in pyrimidine and purine use in coding sequences, the strand with the greater coding content will tend to have the greater number of purine bases (Szybalski's rule). Because the number of purine bases will to a very good approximation equal the number of their complementary pyrimidines within the same strand and because the coding sequences occupy 80-90% of the strand,

there appears to be (1) a selective pressure on the third base to minimize the number of purine bases in the strand with the greater coding content and (2) that this pressure is proportional to the mismatch in the length of the coding sequences between the two strands.

The origin of the deviation from Chargaff's rule in the organelles has been suggested to be a consequence of the mechanism of replication.[14] During replication the DNA strands separate. In single stranded DNA, cytosine spontaneously slowly deaminates to adenosine (a C to A transversion). The longer the strands are separated the greater the quantity of deamination. For reasons that are not yet clear the strands tend to exist longer in single form in mitochondria than in chromsomal DNA. This process tends to yield one strand that is enriched in guanine (G) and thymine (T) with its complement enriched in cytosine (C) and adenosine (A) and this process may have given rise to the deviations found in the mitochondria.

Chargaff's second rule appears to be the consequence of a more complex parity rule: within a single strand of DNA any oligonucleotide is present in equal numbers to its reverse complementary nucleotide. Because of the computational requirements this has not been verified in all genomes for all oligonucleotides. It has been verified for triplet oligonucleotides for a large data set.[15] Albrecht-Buehler has suggested that this rule is the consequence of genomes evolving by a process of inversion and transposition. This process does not appear to have acted on the mitochondrial genomes.

Relative proportions (%) of bases in DNA

The following table is a representative sample of Erwin Chargaff's 1952 data, listing the base composition of DNA from various organisms a support both of Chargaff's rules.[16]

Organism	%A	%G	%C	%T	A/T	G/C	%GC
φX174	24.0	23.3	21.5	31.2	0.77	1.08	44.8
Maize	26.8	22.8	23.2	27.2	0.99	0.98	46.1
Octopus	33.2	17.6	17.6	31.6	1.05	1.00	35.2
Chicken	28.0	22.0	21.6	28.4	0.99	1.02	43.7
Rat	28.6	21.4	20.5	28.4	1.01	1.00	42.9
Human	29.3	20.7	20.0	30.0	0.98	1.04	40.7
Grasshopper	29.3	20.5	20.7	29.3			
Sea Urchin	32.8	17.7	17.3	32.1			
Wheat	27.3	22.7	22.8	27.1			
Yeast	31.3	18.7	17.1	32.9			
E. Coli	24.7	26.0	25.7	23.6			

See also

- CBS Genome Atlas Database [17] — contains hundreds of examples of base skews.[18]
- The Z curve database of genomes [19] — a 3-dimensional visualization and analysis tool of genomes.[8]

Further reading

- Szybalski W, Kubinski H, Sheldrick P (1966). "Pyrimidine clusters on the transcribing strands of DNA and their possible role in the initiation of RNA synthesis". *Cold Spring Harbor NY Symp. Quant Biol* **31**: 123−127.
- Lobry JR (1996). "Asymmetric substitution patterns in the two DNA strands of bacteria". *Mol. Biol. Evol.* **13**: 660−665.
- Lafay B, Lloyd AT, McLean MJ, Devine KM, Sharp PM, Wolfe KH (1999). "Proteome composition and codon usage in spirochaetes: species-specific and DNA strand-specific mutational biases". *Nucleic Acids Res* **27**: 1642−1649.
- McLean MJ, Wolfe KH, Devine KM (1998). "Base composition skews, replication orientation, and gene orientation in 12 prokaryote genomes". *J Mol Evol* **47** (6): 691−696. PMID 9847411 [20].
- McInerney JO (1998). "Replicational and transcriptional selection on codon usage in Borrelia burgdorferi". *Proc Natl Acad Sci USA* **95**: 10698−10703.

References

[1] Elson D, Chargaff E (1952). "On the deoxyribonucleic acid content of sea urchin gametes". *Experientia* **8** (4): 143−145.

[2] Chargaff E, Lipshitz R, Green C (1952). "Composition of the deoxypentose nucleic acids of four genera of sea-urchin". *J Biol Chem* **195** (1): 155−160. PMID 14938364 (http://www.ncbi.nlm.nih.gov/pubmed/14938364).

[3] Chargaff E, Lipshitz R, Green C, Hodes ME (1951). "The composition of the deoxyribonucleic acid of salmon sperm". *J Biol Chem* **192** (1): 223−230. PMID 14917668 (http://www.ncbi.nlm.nih.gov/pubmed/14917668).

[4] Chargaff E (1951). "Some recent studies on the composition and structure of nucleic acids". *J Cell Physiol Suppl* **38** (Suppl).

[5] Magasanik B, Vischer E, Doniger R, Elson D, Chargaff E (1950). "The separation and estimation of ribonucleotides in minute quantities". *J Biol Chem* **186** (1): 37−50. PMID 14778802 (http://www.ncbi.nlm.nih.gov/pubmed/14778802).

[6] Chargaff E (1950). "Chemical specificity of nucleic acids and mechanism of their enzymatic degradation". *Experientia* **6** (6): 201−209.

[7] Rudner R, Karkas JD, Chargaff E (1968). Separation of *B. subtilis* DNA into complementary strands. III. Direct Analysis. *Proc Natl Acad Sci USA, 60:921-922.* PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=retrieve&db=pubmed&list_uids=4970114&dopt=Abstract)

[8] Zhang CT, Zhang R, Ou HY (2003). "The Z curve database: a graphic representation of genome sequences". *Bioinformatics* **19** (5): 593−599. doi: 10.1093/bioinformatics/btg041 (http://dx.doi.org/10.1093/bioinformatics/btg041).

[9] Mitchell D, Bridge R (2006). A test of Chargaff's second rule. *Biochem Biophys Res Commun, 340(1):90-94.*

[10] Szybalski W, Kubinski H, Sheldrick O (1966). Pyrimidine clusters on the transcribing strand of DNA and their possible role in the initiation of RNA synthesis. *Cold Spring Harbor Symp Quant Biol, 31:123-127.*

[11] Cristillo AD (1998). "Characterization of G0/G1 switch genes in cultured T lymphocytes". PhD thesis. Queen's University, Kingston, Ontario Canada.

[12] Bell SJ, Forsdyke DR (1999). Deviations from Chargaff's second parity rule correlate with direction of transcription. *J Theor Biol, 197:63-76.*

[13] Lao PJ, Forsdyke DR (2000). Thermophilic Bacteria Strictly Obey Szybalski's Transcription Direction Rule and Politely Purine-Load RNAs with Both Adenine and Guanine. *Genome, 10(2):228-236.*

[14] Nikolaou C, Almirantis Y (2006). Deviations from Chargaff's second parity rule in organellar DNA. Insights into the evolution of organellar genomes. *Gene, 381:34-41.*

[15] Albrecht-Buehler G (2006). Asymptotically increasing compliance of genomes with Chargaff's second parity rules through inversions and inverted transpositions. *Proc Natl Acad Sci USA 103 (47) 17828-17833*

[16] Bansal M (2003). "DNA structure: Revisiting the Watson-Crick double helix" (http://www.ias.ac.in/currsci/dec102003/1556.pdf). *Current Science* **85** (11): 1556−1563. .

[17] http://www.cbs.dtu.dk/services/GenomeAtlas/

[18] Hallin PF, David Ussery D (2004). "CBS Genome Atlas Database: A dynamic storage for bioinformatic results and sequence data". *Bioinformatics* **20**: 3682−3686.

[19] http://tubic.tju.edu.cn/zcurve/

[20] http://www.ncbi.nlm.nih.gov/pubmed/9847411

Double helix

In geometry a **double helix** (plural *helices*) typically consists of two congruent helices with the same axis, differing by a translation along the axis, which may or may not be half-way.[1]

The term "double helix" is commonly encountered in molecular biology, where it refers to the structure of DNA. The double-helix model of DNA structure was first published in the journal Nature by James D. Watson and Francis Crick in 1953[2] , based upon the crucial X-ray diffraction image of DNA (labeled as "Photo 51") from Rosalind Franklin in 1952 [3] , followed by her more clarified DNA image with Raymond Gosling[4] [5] , Maurice Wilkins, Alexander Stokes and Herbert Wilson[6] , as well as base-pairing chemical and biochemical information by Erwin Chargaff[7] [8] [9] [10] [11] [12] .

Crick, Wilkins and Watson each received one third of the 1962 Nobel Prize in Physiology or Medicine for their contributions to the discovery[13] . (Franklin, whose breakthrough X-ray diffraction data was used to formulate the DNA structure, died in 1958, and thus was ineligible to be nominated for a Nobel Prize.)

The DNA double helix is a right-handed spiral polymer of nucleic acids, held together by nucleotides which base pair together[14] . A single turn of the helix constitutes ten nucleotides[14] . The double helix structure of DNA contains a major groove and minor groove, the major groove being wider than the minor groove[14] . Given the difference in widths of the major groove and minor groove, many proteins which bind to DNA do so through the wider major groove [15] .

The order, or sequence, of the nucleotides in the double helix within a gene specifies the primary structure of a protein.

The term entered popular culture with the publication in 1968 of *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, by James Watson.

See also

• Molecular structure of Nucleic Acids

A staircase in the shape of a double helix, in the Vatican Museum
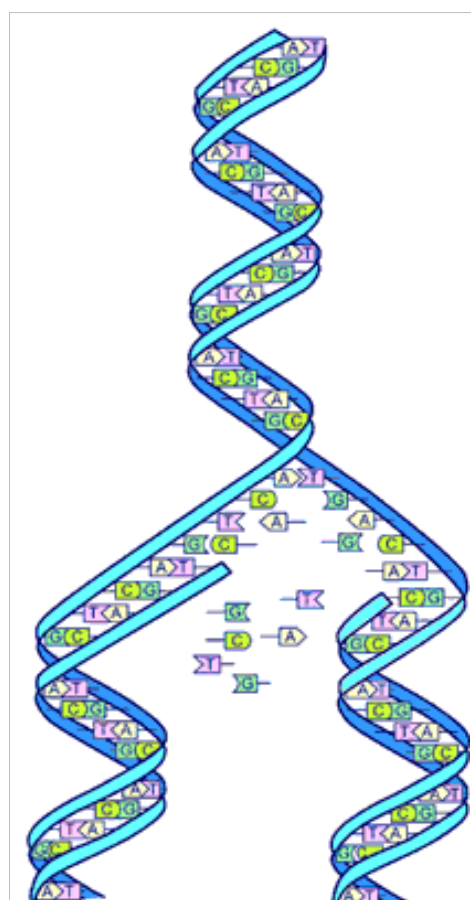
Image of a DNA chain which shows the double helix replicating itself

References

[1] "Double Helix" (http://demonstrations.wolfram.com/DoubleHelix/) by Sándor Kabai, The Wolfram Demonstrations Project, 2007.

[2] James D. Watson and Francis Crick (1953). "A structure for deoxyribose nucleic acid" (http://www.nature.com/nature/dna50/watsoncrick.pdf). *Nature* **171**: 737−8. doi: 10.1038/171737a0 (http://dx.doi.org/10.1038/171737a0). .

[3] http://www.pbs.org/wgbh/nova/photo51/

[4] http://www.nature.com/nature/dna50/franklingosling.pdf

[5] The Structure of the DNA Molecule (http://www.accessexcellence.org/AE/AEC/CC/DNA_structure.php)

[6] Wilkins M.H.F., A.R. Stokes A.R. & Wilson, H.R. (1953). "Molecular Structure of Deoxypentose Nucleic Acids" (http://www.nature.com/nature/dna50/wilkins.pdf) (PDF). *Nature* **171**: 738−740. doi: 10.1038/171738a0 (http://dx.doi.org/10.1038/171738a0). PMID 13054693 (http://www.ncbi.nlm.nih.gov/pubmed/13054693). .

[7] Elson D, Chargaff E (1952). "On the deoxyribonucleic acid content of sea urchin gametes". *Experientia* **8** (4): 143−145.

[8] Chargaff E, Lipshitz R, Green C (1952). "Composition of the deoxypentose nucleic acids of four genera of sea-urchin". *J Biol Chem* **195** (1): 155−160. PMID 14938364 (http://www.ncbi.nlm.nih.gov/pubmed/14938364).

[9] Chargaff E, Lipshitz R, Green C, Hodes ME (1951). "The composition of the deoxyribonucleic acid of salmon sperm". *J Biol Chem* **192** (1): 223−230. PMID 14917668 (http://www.ncbi.nlm.nih.gov/pubmed/14917668).

[10] Chargaff E (1951). "Some recent studies on the composition and structure of nucleic acids". *J Cell Physiol Suppl* **38** (Suppl).

[11] Magasanik B, Vischer E, Doniger R, Elson D, Chargaff E (1950). "The separation and estimation of ribonucleotides in minute quantities". *J Biol Chem* **186** (1): 37−50. PMID 14778802 (http://www.ncbi.nlm.nih.gov/pubmed/14778802).

[12] Chargaff E (1950). "Chemical specificity of nucleic acids and mechanism of their enzymatic degradation". *Experientia* **6** (6): 201−209.

[13] "Nobel Prize - List of All Nobel Laureates" (http://nobelprize.org/nobel_prizes/lists/all/). .

[14] Alberts et al. (1994). *The Molecular Biology of the Cell*. New York: Garland Science. ISBN 978-0815341055.

[15] Pabo C, Sauer R (1984). "Protein-DNA recognition". *Annu Rev Biochem* **53**: 293−321. doi: 10.1146/annurev.bi.53.070184.001453 (http://dx.doi.org/10.1146/annurev.bi.53.070184.001453). PMID 6236744 (http://www.ncbi.nlm.nih.gov/pubmed/6236744).

DNA structure

The structure of DNA shows a variety of forms, both double-stranded and single-stranded. The mechanical properties of DNA, which are directly related to its structure, are a significant problem for cells. Every process which binds or reads DNA is able to use or modify the mechanical properties of DNA for purposes of recognition, packaging and modification. The extreme length (a chromosome may contain a 10 cm long DNA strand), relative rigidity and helical structure of DNA has led to the evolution of histones and of enzymes such as topoisomerases and helicases to manage a cell's DNA. The properties of DNA are closely related to its molecular structure and sequence, particularly the weakness of the hydrogen bonds and electronic interactions that hold strands of DNA together compared to the strength of the bonds within each strand.

Experimental techniques which can directly measure the mechanical properties of DNA are relatively new, and high-resolution visualization in solution is often difficult. Nevertheless, scientists have uncovered large amount of data on the mechanical properties of this polymer, and the implications of DNA's mechanical properties on cellular processes is a topic of active current research.

The DNA found in many cells can be macroscopic in length - a few centimetres long for each human chromosome. Consequently, cells must compact or "package" DNA to carry it within them. In eukaryotes this is carried by spool-like proteins known as histones, around which DNA winds. It is the further compaction of this DNA-protein complex which produces the well known mitotic eukaryotic chromosomes.

Structure determination

DNA structures can be determined using either nuclear magnetic resonance spectroscopy or X-ray crystallography. The first published reports of A-DNA X-ray diffraction patterns-- and also B-DNA—employed analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA isolated from calf thymus.[1] [2] An alternate analysis was then proposed by Wilkins et al. in 1953 for B-DNA X-ray diffraction/scattering patterns of hydrated, bacterial oriented DNA fibers and trout sperm heads in terms of squares

of Bessel functions.[3] Although the `B-DNA form' is most common under the conditions found in cells,[4] it is not a well-defined conformation but a family or fuzzy set of DNA-conformations that occur at the high hydration levels present in a wide variety of living cells.[5] Their corresponding X-ray diffraction & scattering patterns are characteristic of molecular paracrystals with a significant degree of disorder (>20%)[6] [7] , and concomitantly the structure is not tractable using only the standard analysis.

On the other hand, the standard analysis, involving only Fourier transforms of Bessel functions[8] and DNA molecular models, is still routinely employed for the analysis of A-DNA and Z-DNA X-ray diffraction patterns.[9]

Base pair geometry

The geometry of a base, or base pair step can be characterized by 6 coordinates: Shift, Slide, Rise, Tilt, Roll, and Twist. These values precisely define the location and orientation in space of every base or base pair in a DNA molecule relative to its predecessor along the axis of the helix. Together, they characterize the helical structure of the molecule. In regions of DNA where the "normal" structure is disrupted the change in these values can be used to describe such disruption.

For each base pair, considered relative to its predecessor[10] [11] [12] :

- Shear

- Stretch

- Stagger

- Buckle

- Propeller twist: *Rotation of one base with respect to the other in the same base pair.*

- Opening

- Shift: *displacement along an axis in the base-pair plane perpendicular to the first, directed from the minor to the major groove.*

- Slide: *displacement along an axis in the plane of the base pair directed from one strand to the other.*

- Rise: *displacement along the helix axis.*

- Tilt: *rotation around this axis.*

- Roll: *rotation around this axis.*

- Twist: *rotation around the helix axis.*

- x-displacement

- y-displacement

- inclination

- tip

- pitch: *the number of base pairs per complete turn of the helix*

Rise and twist determine the handedness and pitch of the helix. The other coordinates, by contrast, can be zero. Slide and shift are typically small in B-DNA, but are substantial in A- and Z-DNA. Roll and tilt make successive base pairs less parallel, and are typically small. A diagram [13] of these coordinates can be found in 3DNA [14] website.

Note that "tilt" has often been used differently in the scientific literature, referring to the deviation of the first, inter-strand base-pair axis from perpendicularity to the helix axis. This corresponds to slide between a succession of base pairs, and in helix-based coordinates is properly termed "inclination".

DNA helix geometries

Three DNA conformations are believed to be found in nature, A-DNA, B-DNA, and Z-DNA. The "B" form described by James D. Watson and Francis Crick is believed to predominate in cells[15] . It is 23.7 Å wide and extends 34 Å per 10 bp of sequence. The double helix makes one complete turn about its axis every 10.4-10.5 base pairs in solution. This frequency of twist (known as the helical *pitch*) depends largely on stacking forces that each base exerts on its neighbours in the chain. The magnitude of the twist of B-DNA has been found to conincide with the magnitude of the intrinsic angular momentum of photons[16] .

Other conformations are possible; A-DNA, B-DNA, C-DNA, D-DNA[17] , E-DNA[18] , L-DNA(enantiomeric form of D-DNA)[17] , P-DNA[19] , S-DNA, Z-DNA, etc. have been described so far.[20] In fact, only the letters F, Q, U, V, and Y are now available to describe any new DNA structure that may appear in the future.[21] [22] However, most of these forms have been created synthetically and have not been observed in naturally occurring biological systems. Also note the triple-stranded DNA possibility.

A- and Z-DNA

A-DNA and Z-DNA differ significantly in their geometry and dimensions to B-DNA, although still form helical structures. The A form appears likely to occur only in dehydrated samples of DNA, such as those used in crystallographic experiments, and possibly in hybrid pairings of DNA and RNA strands. Segments of DNA that cells have methylated for regulatory purposes may adopt the Z geometry, in which the strands turn about the helical axis the opposite way to A-DNA and B-DNA. There is also evidence of protein-DNA complexes forming Z-DNA structures.

The structures of A-, B-, and Z-DNA.

The helix axis of A-, B-, and Z-DNA.
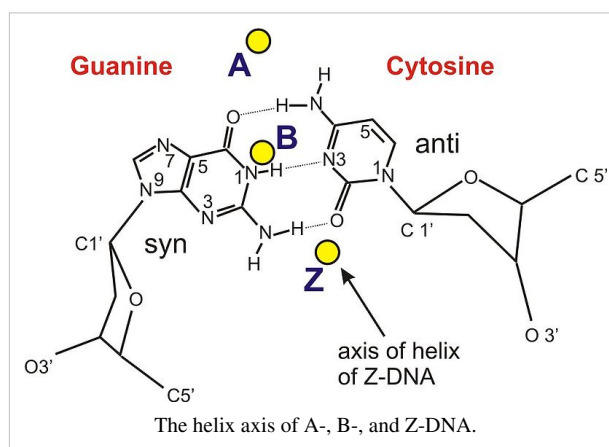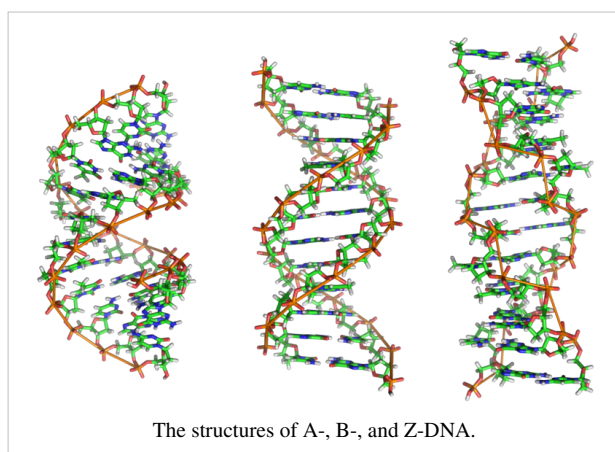
Structural features of the three major forms of DNA

Geometry attribute	A-DNA	B-DNA	Z-DNA
Helix sense	right-handed	right-handed	left-handed
Repeating unit	1 bp	1 bp	2 bp
Rotation/bp	33.6°	35.9°	60°/2bp
Mean bp/turn	10.7	10.0	12
Inclination of bp to axis	+19°	-1.2°	-9°
Rise/bp along axis	2.3 Å	3.32 Å	3.8 Å
Pitch/turn of helix	24.6 Å	33.2 Å	45.6 Å
Mean propeller twist	+18°	+16°	0°

Glycosyl angle	anti	anti	**C**: anti, **G**: syn
Sugar pucker	C3'-endo	C2'-endo	**C**: C2'-endo, **G**: C2'-exo
Diameter	25.5 Å	23.7 Å	18.4 Å

Supercoiled DNA

The B form of the DNA helix twists 360° per 10.4-10.5 bp in the absence of torsional strain. But many molecular biological processes can induce torsional strain. A DNA segment with excess or insufficient helical twisting is referred to, respectively, as positively or negatively "supercoiled". DNA *in vivo* is typically negatively supercoiled, which facilitates the unwinding (melting) of the double-helix required for RNA transcription.

Non-helical forms

Other non-double helical forms of DNA have been described, for example side-by-side (SBS) and triple helical configurations. Single stranded DNA may exist *in statu nascendi* or as thermally induced despiralized DNA.

DNA bending

DNA is a relatively rigid polymer, typically modelled as a worm-like chain. It has three significant degrees of freedom; bending, twisting and compression, each of which cause particular limitations on what is possible with DNA within a cell. Twisting/torsional stiffness is important for the circularisation of DNA and the orientation of DNA bound proteins relative to each other and bending/axial stiffness is important for DNA wrapping and circularisation and protein interactions. Compression/extension is relatively unimportant in the absence of high tension.

Persistence length/Axial stiffness

Example sequences and their persistence lengths (B DNA)

Sequence	Persistence Length /base pairs
Random	154±10
(CA)$_{repeat}$	133±10
(CAG)$_{repeat}$	124±10
(TATA)$_{repeat}$	137±10

DNA in solution does not take a rigid structure but is continually changing conformation due to thermal vibration and collisions with water molecules, which makes classical measures of rigidity impossible. Hence, the bending stiffness of DNA is measured by the persistence length, defined as:

> "The length of DNA over which the time-averaged orientation of the polymer becomes uncorrelated by a factor of *e*."

This value may be directly measured using an atomic force microscope to directly image DNA molecules of various lengths. In aqueous solution the average persistence length is 46-50 nm or 140-150 base pairs (the diameter of DNA is 2 nm), although can vary significantly. This makes DNA a moderately stiff molecule.

The persistence length of a section of DNA is somewhat dependent on its sequence, and this can cause significant variation. The variation is largely due to base stacking energies and the residues which extend into the minor and major grooves.

Models for DNA bending

Stacking stability of base steps (B DNA)

Step	Stacking ΔG /kcal mol^{-1}
T A	-0.19
T G or **C A**	-0.55
C G	-0.91
A G or **C T**	-1.06
A A or **T T**	-1.11
A T	-1.34
G A or **T C**	-1.43
C C or **G G**	-1.44
A C or **G T**	-1.81
G C	-2.17

The entropic flexibility of DNA is remarkably consistent with standard polymer physics models such as the *Kratky-Porod* worm-like chain model. Consistent with the worm-like chain model is the observation that bending DNA is also described by Hooke's law at very small (sub-piconewton) forces. However for DNA segments less than the persistence length, the bending force is approximately constant and behaviour deviates from the worm-like chain predictions.
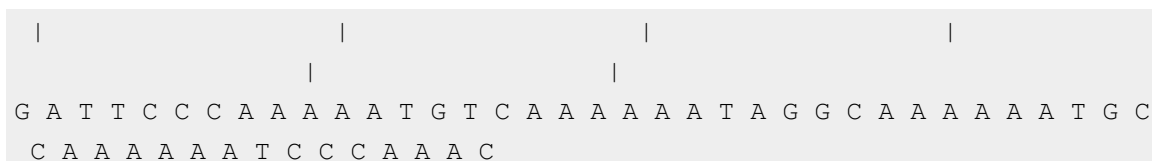
This effect results in unusual ease in circularising small DNA molecules and a higher probability of finding highly bent sections of DNA.

Bending preference

DNA molecules often have a preferred direction to bend, ie. anisotropic bending. This is, again, due to the properties of the bases which make up the DNA sequence - a random sequence will have no preferred bend direction, i.e. isotropic bending.

Preferred DNA bend direction is determined by the stability of stacking each base on top of the next. If unstable base stacking steps are always found on one side of the DNA helix then the DNA will preferentially bend away from that direction. As bend angle increases then steric hindrances and ability to roll the residues relative to each other also play a role, especially in the minor groove. **A** and **T** residues will be preferentially be found in the minor grooves on the inside of bends. This effect is particularly seen in DNA-protein binding where tight DNA bending is induced, such as in nucleosome particles. See base step distortions above.

DNA molecules with exceptional bending preference can become intrinsically bent. This was first observed in trypanosomatid kinetoplast DNA. Typical sequences which cause this contain stretches of 4-6 **T** and **A** residues separated by **G** and **C** rich sections which keep the A and T residues in phase with the minor groove on one side of the molecule. For example:

```
  |                          |                        |                          |
                  |                        |
G A T T C C C A A A A A T G T C A A A A A A T A G G C A A A A A A T G C
 C A A A A A A T C C C A A A C
```

The intrinsically bent structure is induced by the 'propeller twist' of base pairs relative to each other allowing unusual bifurcated Hydrogen-bonds between base steps. At higher temperatures this structure, and so the intrinsic bend, is lost.

All DNA which bends anisotropically has, on average, a longer persistence length and greater axial stiffness. This increased rigidity is required to prevent random bending which would make the molecule act isotropically.

DNA circularization

DNA circularization depends on both the axial (bending) stiffness and torsional (rotational) stiffness of the molecule. For a DNA molecule to successfully circularize it must be long enough to easily bend into the full circle and must have the correct number of bases so the ends are in the correct rotation to allow bonding to occur. The optimum length for circularization of DNA is around 400 base pairs (136 nm), with an integral number of turns of the DNA helix, i.e. multiples of 10.4 base pairs. Having a non integral number of turns presents a significant energy barrier for circularization, for example a 10.4 x 30 = 312 base pair molecule will circularize hundreds of times faster than 10.4 x 30.5 ≈ 317 base pair molecule.

DNA stretching

Longer stretches of DNA are entropically elastic under tension. When DNA is in solution, it undergoes continuous structural variations due to the energy available in the solvent. This is due to the thermal vibration of the molecule combined with continual collisions with water molecules. For entropic reasons, more compact relaxed states are thermally accessible than stretched out states, and so DNA molecules are almost universally found in a tangled relaxed layouts. For this reason, a single molecule of DNA will stretch under a force, straightening it out. Using optical tweezers, the entropic stretching behavior of DNA has been studied and analyzed from a polymer physics perspective, and it has been found that DNA behaves largely like the *Kratky-Porod* worm-like chain model under physiologically accessible energy scales.

Under sufficient tension and positive torque, DNA is thought to undergo a phase transition with the bases splaying outwards and the phosphates moving to the middle. This proposed structure for overstretched DNA has been called "P-form DNA," in honor of Linus Pauling who originally presented it as a possible structure of DNA[19]

The mechanical properties DNA under compression have not been characterized due to experimental difficulties in preventing the polymer from bending under the compressive force.

DNA melting

Melting stability of base steps (B DNA)

Step	Melting ΔG /Kcal mol^{-1}
T A	-0.12
T G or **C A**	-0.78
C G	-1.44
A G or **C T**	-1.29
A A or **T T**	-1.04
A T	-1.27
G A or **T C**	-1.66
C C or **G G**	-1.97
A C or **G T**	-2.04
G C	-2.70

DNA melting is the process by which the interactions between the strands of the double helix are broken, separating the two strands of DNA. These bonds are weak, easily separated by gentle heating, enzymes, or physical force. DNA melting preferentially occurs at certain points in the DNA.[23] **T** and **A** rich sequences are more easily melted than **C** and **G** rich regions. Particular base steps are also susceptible to DNA melting, particularly **T A** and **T G** base steps.[24] These mechanical features are reflected by the use of sequences such as **TATAA** at the start of many genes to assist RNA polymerase in melting the DNA for transcription.

Strand separation by gentle heating, as used in PCR, is simple providing the molecules have fewer than about 10,000 base pairs (10 kilobase pairs, or 10 kbp). The intertwining of the DNA strands makes long segments difficult to separate. The cell avoids this problem by allowing its DNA-melting enzymes (helicases) to work concurrently with topoisomerases, which can chemically cleave the phosphate backbone of one of the strands so that it can swivel around the other. Helicases unwind the strands to facilitate the advance of sequence-reading enzymes such as DNA polymerase.

DNA topology

Within the cell most DNA is topologically restricted. DNA is typically found in closed loops (such as plasmids in prokaryotes) which are topologically closed, or as very long molecules whose diffusion coefficients produce effectively topologically closed domains. Linear sections of DNA are also commonly bound to proteins or physical structures (such as membranes) to form closed topological loops.

Francis Crick was one of the first to propose the importance of linking numbers when considering DNA supercoils. In a paper published in 1976, Crick outlined the problem as follows:

> In considering supercoils formed by closed double-stranded molecules of DNA certain mathematical concepts, such as the linking number and the twist, are needed. The meaning of these for a closed ribbon is explained and also that of the writhing number of a closed curve. Some simple examples are given, some of which may be relevant to the structure of chromatin.[25]

Analysis of DNA topology uses three values:

> L = linking number - the number of times one DNA strand wraps around the other. It is an integer for a closed loop and constant for a closed topological domain.

> T = twist - total number of turns in the double stranded DNA helix. This will normally try to be equal to the number turns a DNA molecule will make while free in solution, ie. number of bases/10.4.

> W = writhe - number of turns of the double stranded DNA helix around the superhelical axis

> $L = T + W$ and $\Delta L = \Delta T + \Delta W$

Supercoiled structure of circular DNA molecules with low writhe. Note that the helical nature of the DNA duplex is omitted for clarity.

Any change of T in a closed topological domain must be balanced by a change in W, and vice versa. This results in higher order structure of DNA. A circular DNA molecule with a writhe of 0 will be circular. If the twist of this molecule is subsequently increased or decreased by supercoiling then the writhe will be appropriately altered, making the molecule undergo plectonemic or toroidal superhelical coiling.

When the ends of a piece of double stranded helical DNA are joined so that it forms a circle the strands are topologically knotted. This means the single strands cannot be separated any process that does not involve breaking a strand (such as heating). The task of un-knotting topologically linked strands of DNA falls to enzymes known as topoisomerases. These enzymes are dedicated to un-knotting circular DNA by cleaving one or both strands so that another double or single stranded segment can pass through. This un-knotting is required for the replication of circular DNA and various types of recombination in linear DNA which have similar topological constraints.
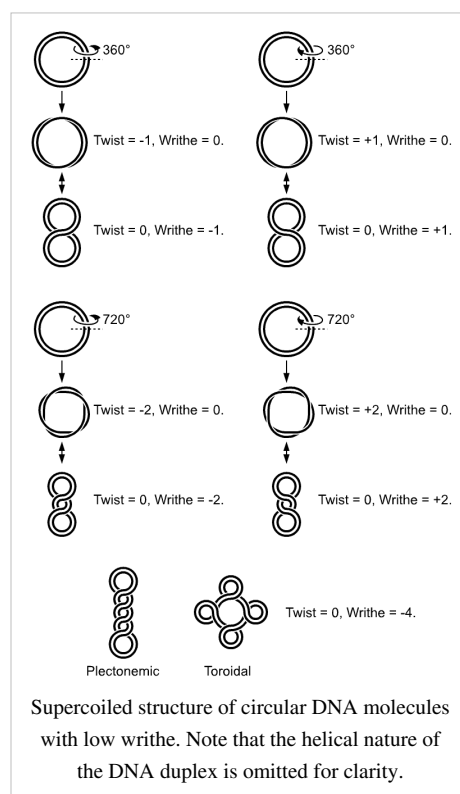
The linking number paradox

For many years, the origin of residual supercoiling in eukaryotic genomes remained unclear. This topological puzzle was referred to by some as the "linking number paradox".[26] However, when experimentally determined structures of the nucleosome displayed an overtwisted left-handed wrap of DNA around the histone octamer[27] [28] , this "paradox" was solved.

See also

- DNA nanotechnology
- Molecular models of DNA

External links

- MDDNA: Structural Bioinformatics of DNA [29]
- Abalone [30] — Commercial software for DNA modeling
- DNAlive: a web interface to compute DNA physical properties [31]. Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database [32]. The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.

References

[1] Franklin, R.E. and Gosling, R.G. received 6 March 1953. *Acta Cryst*. (1953). **6**, 673: The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content.; also *Acta Cryst*. **6**, 678: The Structure of Sodium Thymonucleate Fibres II. The Cylindrically Symmetrical Patterson Function.

[2] Franklin, Rosalind (1953). "Molecular Configuration in Sodium Thymonucleate. Franklin R. and Gosling R.G" (http://www.nature.com/nature/dna50/franklingosling.pdf) (PDF). *Nature* **171**: 740–741. doi: 10.1038/171740a0 (http://dx.doi.org/10.1038/171740a0). PMID 13054694 (http://www.ncbi.nlm.nih.gov/pubmed/13054694). .

[3] Wilkins M.H.F., A.R. Stokes A.R. & Wilson, H.R. (1953). "Molecular Structure of Deoxypentose Nucleic Acids" (http://www.nature.com/nature/dna50/wilkins.pdf) (PDF). *Nature* **171**: 738–740. doi: 10.1038/171738a0 (http://dx.doi.org/10.1038/171738a0). PMID 13054693 (http://www.ncbi.nlm.nih.gov/pubmed/13054693). .

[4] Leslie AG, Arnott S, Chandrasekaran R, Ratliff RL (1980). "Polymorphism of DNA double helices". *J. Mol. Biol.* **143** (1): 49–72. doi: 10.1016/0022-2836(80)90124-2 (http://dx.doi.org/10.1016/0022-2836(80)90124-2). PMID 7441761 (http://www.ncbi.nlm.nih.gov/pubmed/7441761).

[5] Baianu, I.C. (1980). "Structural Order and Partial Disorder in Biological systems". *Bull. Math. Biol.* **42** (4): 464–468. doi: 10.1016/0022-2836(80)90124-2 (http://dx.doi.org/10.1016/0022-2836(80)90124-2).

[6] Hosemann R., Bagchi R.N., *Direct analysis of diffraction by matter*, North-Holland Publs., Amsterdam – New York, 1962

[7] Baianu I.C., X-ray scattering by partially disordered membrane systems, *Acta Cryst. A*, **34** (1978), 751–753.

[8] Bessel functions and diffraction by helical structures (http://planetphysics.org/encyclopedia/BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures.html)

[9] X-Ray Diffraction Patterns of Double-Helical Deoxyribonucleic Acid (DNA) Crystals (http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)

[10] Dickerson RE (1989). "Definitions and nomenclature of nucleic acid structure components". *Nucleic Acids Res* **17** (5): 1797–1803. doi: 10.1093/nar/17.5.1797 (http://dx.doi.org/10.1093/nar/17.5.1797). PMID 2928107 (http://www.ncbi.nlm.nih.gov/pubmed/2928107).

[11] Lu XJ, Olson WK (1999). "Resolving the discrepancies among nucleic acid conformational analyses". *J Mol Biol* **285** (4): 1563–1575. doi: 10.1006/jmbi.1998.2390 (http://dx.doi.org/10.1006/jmbi.1998.2390). PMID 9917397 (http://www.ncbi.nlm.nih.gov/pubmed/9917397).

[12] Olson WK, Bansal M, Burley SK, Dickerson RE, Gerstein M, Harvey SC, Heinemann U, Lu XJ, Neidle S, Shakked Z, Sklenar H, Suzuki M, Tung CS, Westhof E, Wolberger C, Berman HM (2001). "A standard reference frame for the description of nucleic acid base-pair geometry". *J Mol Biol* **313** (1): 229–237. doi: 10.1006/jmbi.2001.4987 (http://dx.doi.org/10.1006/jmbi.2001.4987). PMID 11601858 (http://www.ncbi.nlm.nih.gov/pubmed/11601858).

[13] http://rutchem.rutgers.edu/~xiangjun/3DNA/images/bp_step_hel.gif

[14] http://rutchem.rutgers.edu/~xiangjun/3DNA/examples.html

[15] Richmond, et al. (2003). "The structure of DNA in the nucleosome core". *Nature* **423**: 145–150. doi: 10.1038/nature01595 (http://dx.doi.org/10.1038/nature01595). PMID 12736678 (http://www.ncbi.nlm.nih.gov/pubmed/12736678).

[16] El-Khazen S. (2009). "DNA: The Gateway to Time" (http://www.neuroquantology.com/repository/index.php?option=com_sobi2& sobi2Task=sobi2Details&catid=0&sobi2Id=309&Itemid=66). *NeuroQuantology* **7(1)**: 152–175.

[17] Hayashi G, Hagihara M, Nakatani K (2005). "Application of L-DNA as a molecular tag". *Nucleic Acids Symp Ser (Oxf)* **49**: 261–262. PMID 17150733 (http://www.ncbi.nlm.nih.gov/pubmed/17150733).

[18] Vargason JM, Eichman BF, Ho PS (2000). "The extended and eccentric E-DNA structure induced by cytosine methylation or bromination". *Nature Structural Biology* **7**: 758–761. doi: 10.1038/78985 (http://dx.doi.org/10.1038/78985).

[19] Allemand, et al. (1998). "Stretched and overwound DNA forms a Pauling-like structure with exposed bases". *PNAS* **24**: 14152–14157. doi: 10.1073/pnas.95.24.14152 (http://dx.doi.org/10.1073/pnas.95.24.14152). PMID 9826669 (http://www.ncbi.nlm.nih.gov/pubmed/9826669).

[20] List of 55 fiber structures (http://rutchem.rutgers.edu/~xiangjun/3DNA/misc/fiber_model.txt)

[21] Bansal M (2003). "DNA structure: Revisiting the Watson-Crick double helix". *Current Science* **85** (11): 1556–1563.

[22] Ghosh A, Bansal M (2003). "A glossary of DNA structures from A to Z". *Acta Cryst* **D59**: 620–626. doi: 10.1107/S0907444903003251 (http://dx.doi.org/10.1107/S0907444903003251).

[23] Breslauer KJ, Frank R, Blöcker H, Marky LA (1986). "Predicting DNA duplex stability from the base sequence". *PNAS* **83** (11): 3746–3750. PMID 3459152 (http://www.ncbi.nlm.nih.gov/pubmed/3459152).

[24] Richard Owczarzy (2008-08-28). "DNA melting temperature - How to calculate it?" (http://www.owczarzy.net/tm.htm). *High-throughput DNA biophysics*. owczarzy.net. . Retrieved 2008-10-02.

[25] Crick FH (1976). "Linking numbers and nucleosomes". *Proc Natl Acad Sci USA* **73** (8): 2639–43. doi: 10.1073/pnas.73.8.2639 (http://dx.doi.org/10.1073/pnas.73.8.2639). PMID 1066673 (http://www.ncbi.nlm.nih.gov/pubmed/1066673).

[26] Prunell A (1998). "A topological approach to nucleosome structure and dynamics: the linking number paradox and other issues". *Biophys J* **74** (5): 2531–2544. PMID 9591679 (http://www.ncbi.nlm.nih.gov/pubmed/9591679).

[27] Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ (1997). "Crystal structure of the nucleosome core particle at 2.8 A resolution". *Nature* **389** (6648): 251–260. doi: 10.1038/38444 (http://dx.doi.org/10.1038/38444). PMID 9305837 (http://www.ncbi.nlm.nih.gov/pubmed/9305837).

[28] Davey CA, Sargent DF, Luger K, Maeder AW, Richmond TJ (2002). "Solvent mediated interactions in the structure of the nucleosome core particle at 1.9 Å resolution". *Journal of Molecular Biology* **319** (5): 1097–1113. doi: 10.1016/S0022-2836(02)00386-8 (http://dx.doi.org/10.1016/S0022-2836(02)00386-8). PMID 12079350 (http://www.ncbi.nlm.nih.gov/pubmed/12079350).

[29] http://humphry.chem.wesleyan.edu:8080/MDDNA/

[30] http://www.biomolecular-modeling.com/Abalone/index.html

[31] http://mmb.pcb.ub.es/DNAlive

[32] http://diprodb.fli-leibniz.de

Chromosome

A **chromosome** is an organized structure of DNA and protein that is found in cells. It is a single piece of coiled DNA containing many genes, regulatory elements and other nucleotide sequences. Chromosomes also contain DNA-bound proteins, which serve to package the DNA and control its functions. The word *chromosome* comes from the Greek χρῶμα (*chroma*, color) and σῶμα (*soma*, body) due to their property of being very strongly stained by particular dyes.

Chromosomes vary widely between different organisms. The DNA molecule may be circular or linear, and can be composed of 10,000 to 1,000,000,000[1] nucleotides in a long chain. Typically eukaryotic cells (cells with nuclei) have large linear chromosomes and prokaryotic cells (cells without defined nuclei) have smaller circular chromosomes, although there are many exceptions to this rule. Furthermore, cells may contain more than one type of chromosome; for example, mitochondria in most eukaryotes and chloroplasts in plants have their own small chromosomes.

In eukaryotes, nuclear chromosomes are packaged by proteins into a condensed structure called chromatin. This allows the very long DNA molecules to fit into the cell nucleus. The structure of chromosomes and chromatin varies through the cell cycle. Chromosomes are the essential unit for cellular division and must be replicated, divided, and passed successfully to their daughter cells so as to ensure the genetic diversity and survival of their progeny. Chromosomes may exist as either duplicated or unduplicated—unduplicated chromosomes are single linear strands, whereas duplicated chromosomes (copied during synthesis

Diagram of a duplicated and condensed metaphase eukaryotic chromosome. (1) Chromatid − one of the two identical parts of the chromosome after S phase. (2) Centromere − the point where the two chromatids touch, and where the microtubules attach. (3) Short arm. (4) Long arm.

phase) contain two copies joined by a centromere. Compaction of the duplicated chromosomes during mitosis and meiosis results in the classic four-arm structure (pictured to the right). Chromosomal recombination plays a vital role in genetic diversity. If these structures are manipulated incorrectly, through processes known as chromosomal instability and translocation, the cell may undergo mitotic catastrophe and die, or it may aberrantly evade apoptosis leading to the progression of cancer.

In practice "chromosome" is a rather loosely defined term. In prokaryotes and viruses, the term genophore is more appropriate when no chromatin is present. However, a large body of work uses the term chromosome regardless of chromatin content. In prokaryotes DNA is usually arranged as a circle, which is tightly coiled in on itself, sometimes accompanied by one or more smaller, circular DNA molecules called plasmids. These small circular genomes are also found in mitochondria and chloroplasts, reflecting their bacterial origins. The simplest genophores are found in viruses: these DNA or RNA molecules are short linear or circular genophores that often lack structural proteins.
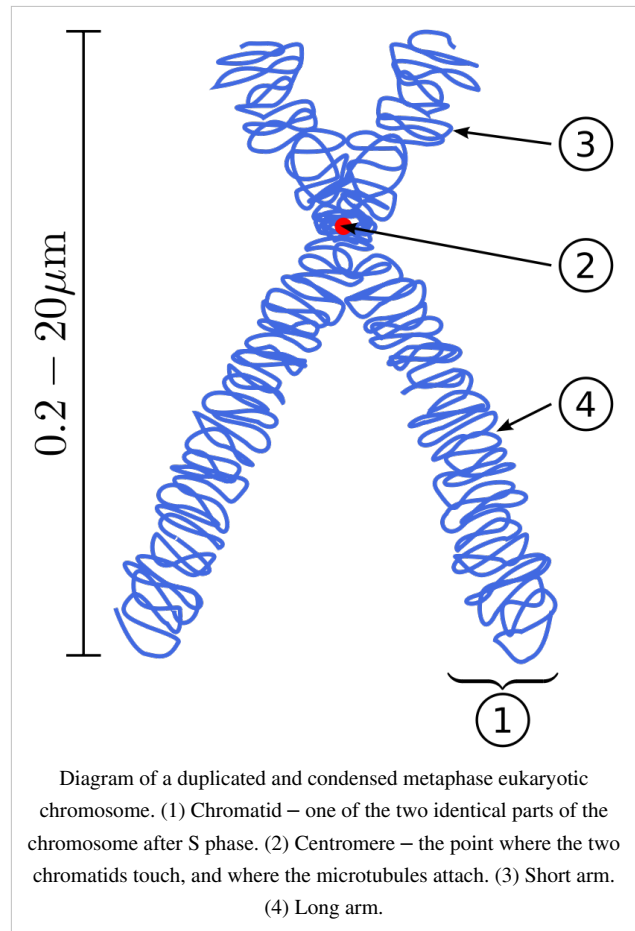
History

Nucleus as the seat of heredity

The origin of this groundbreaking idea lies in a few sentences tucked away in Ernst Haeckel's *Generelle Morphologie* of 1866.[2] The evidence for this insight gradually accumulated until, after twenty or so years, two of the greatest in a line of great German scientists spelled out the concept. August Weismann proposed that the germ line is separate from the soma, and that the cell nucleus is the repository of the hereditary material, which, he proposed, is arranged along the chromosomes in a linear manner. Further, he proposed that at fertilisation a new combination of chromosomes (and their hereditary material) would be formed. This was the explanation for the reduction division of meiosis (first described by van Beneden).

Chromosomes as vectors of heredity

In a series of experiments, Theodor Boveri gave the definitive demonstration that chromosomes are the vectors of heredity. His two principles were based upon the *continuity* of chromosomes and the *individuality* of chromosomes.

It is the second of these principles that was so original. Boveri was able to test the proposal put forward by Wilhelm Roux, that each chromosome carries a different genetic load, and showed that Roux was right. Upon the rediscovery of Mendel, Boveri was able to point out the connection between the rules of inheritance and the behaviour of the chromosomes. It is interesting to see that Boveri influenced two generations of American cytologists: Edmund Beecher Wilson, Walter Sutton and Theophilus Painter were all influenced by Boveri (Wilson and Painter actually worked with him).

In his famous textbook *The Cell*, Wilson linked Boveri and Sutton together by the Boveri-Sutton theory. Mayr remarks that the theory was hotly contested by some famous geneticists: William Bateson, Wilhelm Johannsen, Richard Goldschmidt and T.H. Morgan, all of a rather dogmatic turn-of-mind. Eventually complete proof came from chromosome maps in Morgan's own lab.[3]

Chromosomes in eukaryotes

Eukaryotes (cells with nuclei such as those found in plants, yeast, and animals) possess multiple large linear chromosomes contained in the cell's nucleus. Each chromosome has one centromere, with one or two arms projecting from the centromere, although, under most circumstances, these arms are not visible as such. In addition, most eukaryotes have a small circular mitochondrial genome, and some eukaryotes may have additional small circular or linear cytoplasmic chromosomes.

In the nuclear chromosomes of eukaryotes, the uncondensed DNA exists in a semi-ordered structure, where it is wrapped around histones (structural proteins), forming a composite material called chromatin.

Chromatin

Chromatin is the complex of DNA and protein found in the eukaryotic nucleus, which packages chromosomes. The structure of chromatin varies significantly between different stages of the cell cycle, according to the requirements of the DNA.

Interphase chromatin

During interphase (the period of the cell cycle where the cell is not dividing), two types of chromatin can be distinguished:

- Euchromatin, which consists of DNA that is active, e.g., being expressed as protein.
- Heterochromatin, which consists of mostly inactive DNA. It seems to serve structural purposes during the chromosomal stages. Heterochromatin can be further distinguished into two types:

- *Constitutive heterochromatin*, which is never expressed. It is located around the centromere and usually contains repetitive sequences.
- *Facultative heterochromatin*, which is sometimes expressed.

Individual chromosomes cannot be distinguished at this stage – they appear in the nucleus as a homogeneous tangled mix of DNA and protein.

Metaphase chromatin and division

In the early stages of mitosis or meiosis (cell division), the chromatin strands become more and more condensed. They cease to function as accessible genetic material (transcription stops) and become a compact transportable form. This compact form makes the individual chromosomes visible, and they form the classic four arm structure, a pair of sister chromatids attached to each other at the centromere. The shorter arms are called *p arms* (from the French *petit*, small) and the longer arms are called *q arms* (*q* follows *p* in the Latin alphabet). This is the only natural context in which individual chromosomes are visible with an optical microscope.

During divisions, long microtubules attach to the centromere and the two opposite ends of the cell. The microtubules then pull the chromatids apart, so that each daughter cell inherits one set of chromatids. Once the cells have divided, the chromatids are uncoiled and can function again as chromatin. In spite of their appearance, chromosomes are structurally highly condensed, which enables these giant DNA structures to be contained within a cell nucleus (Fig. 2).
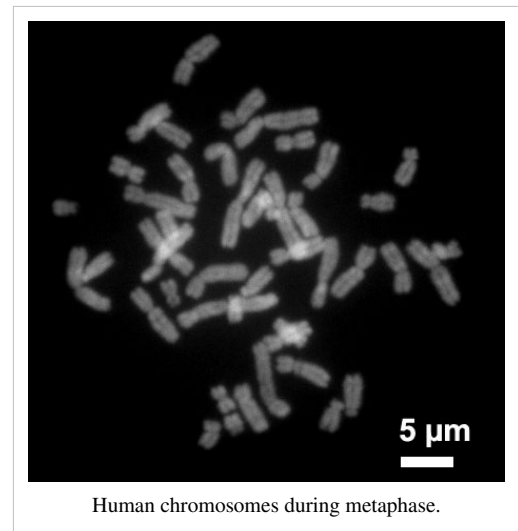
Human chromosomes during metaphase.

The self-assembled microtubules form the spindle, which attaches to chromosomes at specialized structures called kinetochores, one of which is present on each sister chromatid. A special DNA base sequence in the region of the kinetochores provides, along with special proteins, longer-lasting attachment in this region.

Chromosomes in prokaryotes

The prokaryotes – bacteria and archaea – typically have a single circular chromosome, but many variations do exist.[4] Most bacteria have a single circular chromosome that can range in size from only 160,000 base pairs in the endosymbiotic bacterium *Candidatus Carsonella ruddii*,[5] to 12,200,000 base pairs in the soil-dwelling bacterium *Sorangium cellulosum*.[6] Spirochaetes of the genus *Borrelia* are a notable exception to this arrangement, with bacteria such as *Borrelia burgdorferi*, the cause of Lyme disease, containing a single linear chromosome.[7]

Structure in sequences

Prokaryotic chromosomes have less sequence-based structure than eukaryotes. Bacteria typically have a single point (the origin of replication) from which replication starts, whereas some archaea contain multiple replication origins.[8] The genes in prokaryotes are often organized in operons, and do not usually contain introns, unlike eukaryotes.

DNA packaging

Prokaryotes do not possess nuclei. Instead, their DNA is organized into a structure called the nucleoid.[9] The nucleoid is a distinct structure and occupies a defined region of the bacterial cell. This structure is, however, dynamic and is maintained and remodeled by the actions of a range of histone-like proteins, which associate with the bacterial chromosome.[10] In archaea, the DNA in chromosomes is even more organized, with the DNA packaged within

structures similar to eukaryotic nucleosomes.[11] [12]

Bacterial chromosomes tend to be tethered to the plasma membrane of the bacteria. In molecular biology application, this allows for its isolation from plasmid DNA by centrifugation of lysed bacteria and pelleting of the membranes (and the attached DNA).

Prokaryotic chromosomes and plasmids are, like eukaryotic DNA, generally supercoiled. The DNA must first be released into its relaxed state for access for transcription, regulation, and replication.

Fig. 2: The major structures in DNA compaction; DNA, the nucleosome, the 10nm "beads-on-a-string" fibre, the 30nm fibre and the metaphase chromosome.
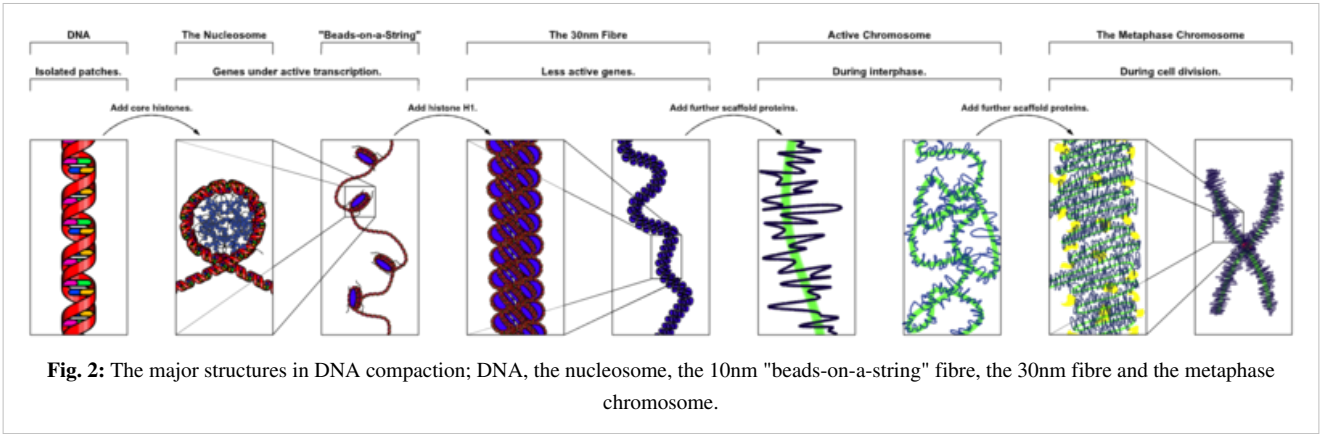
Number of chromosomes in various organisms

Eukaryotes

These tables give the total number of chromosomes (including sex chromosomes) in a cell nucleus. For example, human cells are diploid and have 22 different types of autosome, each present as two copies, and two sex chromosomes. This gives 46 chromosomes in total. Other organisms have more than two copies of their chromosomes, such as bread wheat, which is *hexaploid* and has six copies of seven different chromosomes – 42 chromosomes in total.

Chromosome numbers in some plants

Plant Species	#
Arabidopsis thaliana (diploid)[13]	10
Rye (diploid)[14]	14
Maize (diploid or palaeotetraploid)[15]	20
Einkorn wheat (diploid)[16]	14
Durum wheat (tetraploid)[16]	28
Bread wheat (hexaploid)[16]	42
Cultivated tobacco (tetraploid)[17]	48
Adder's Tongue Fern (diploid)[18]	approx 1,400

Chromosome numbers in other organisms

Species	Large Chromosomes	Intermediate Chromosomes	Microchromosomes
Trypanosoma brucei	11	6	~100
Domestic Pigeon (*Columba livia domestics*)[19]	18	-	59-63
Chicken[20]	8	2 sex chromosomes	60

Normal members of a particular eukaryotic species all have the same number of nuclear chromosomes (see the table). Other eukaryotic chromosomes, i.e., mitochondrial and plasmid-like small chromosomes, are much more variable in number, and there may be thousands of copies per cell.

The 23 human chromosome territories during prometaphase in fibroblast cells.
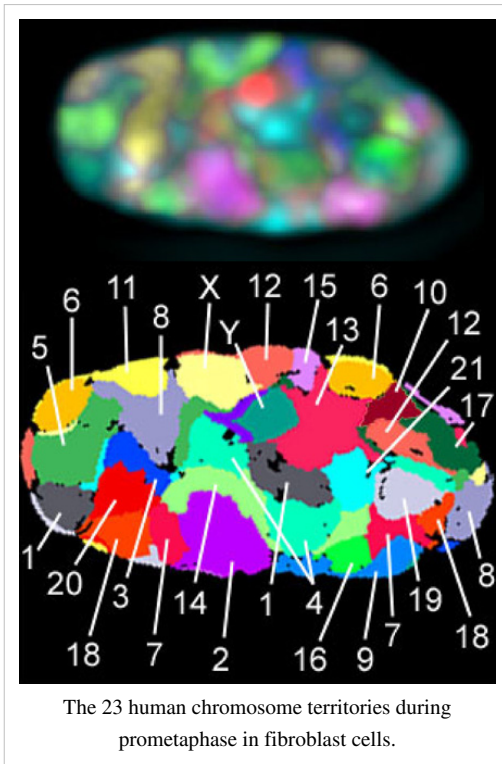
Asexually reproducing species have one set of chromosomes, which are the same in all body cells. However, asexual species can be either haploid or diploid.

Sexually reproducing species have somatic cells (body cells), which are diploid [2n] having two sets of chromosomes, one from the mother and one from the father. Gametes, reproductive cells, are haploid [n]: They have one set of chromosomes. Gametes are produced by meiosis of a diploid germ line cell. During meiosis, the matching chromosomes of father and mother can exchange small parts of themselves (crossover), and thus create new chromosomes that are not inherited solely from either parent. When a male and a female gamete merge (fertilization), a new diploid organism is formed.

Some animal and plant species are polyploid [Xn]: They have more than two sets of homologous chromosomes. Plants important in agriculture such as tobacco or wheat are often polyploid, compared to their ancestral species. Wheat has a haploid number of seven chromosomes, still seen in some cultivars as well as the wild progenitors. The more-common pasta and bread wheats are polyploid, having 28 (tetraploid) and 42 (hexaploid) chromosomes, compared to the 14 (diploid) chromosomes in the wild wheat.[21]

Prokaryotes

Prokaryote species generally have one copy of each major chromosome, but most cells can easily survive with multiple copies.[22] For example, *Buchnera*, a symbiont of aphids has multiple copies of its chromosome, ranging from 10–400 copies per cell.[23] However, in some large bacteria, such as *Epulopiscium fishelsoni* up to 100,000 copies of the chromosome can be present.[24] Plasmids and plasmid-like small chromosomes are, as in eukaryotes, very variable in copy number. The number of plasmids in the cell is almost entirely determined by the rate of division of the plasmid – fast division causes high copy number, and vice versa.

Karyotype

In general, the **karyotype** is the characteristic chromosome complement of a eukaryote species.[25] The preparation and study of karyotypes is part of cytogenetics.

Although the replication and transcription of DNA is highly standardized in eukaryotes, *the same cannot be said for their karyotypes*, which are often highly variable. There may be variation between species in chromosome number and in detailed organization. In some cases, there is significant variation within species. Often there is 1. variation between the two sexes; 2. variation between the germ-line and soma (between gametes and the rest of the body); 3. variation between members of a population, due to balanced genetic polymorphism; 4.

Figure 3: Karyogram of a human male

geographical variation between races; 5. mosaics or otherwise abnormal individuals. Also, variation in karyotype may occur during development from the fertilised egg.

The technique of determining the karyotype is usually called *karyotyping*. Cells can be locked part-way through division (in metaphase) in vitro (in a reaction vial) with colchicine. These cells are then stained, photographed, and arranged into a *karyogram*, with the set of chromosomes arranged, autosomes in order of length, and sex chromosomes (here X/Y) at the end: Fig. 3.

Like many sexually reproducing species, humans have special gonosomes (sex chromosomes, in contrast to autosomes). These are XX in females and XY in males.

Historical note

Investigation into the human karyotype took many years to settle the most basic question. How many chromosomes does a normal diploid human cell contain? In 1912, Hans von Winiwarter reported 47 chromosomes in spermatogonia and 48 in oogonia, concluding an XX/XO sex determination mechanism.[26] Painter in 1922 was not certain whether the diploid number of man is 46 or 48, at first favouring 46.[27] He revised his opinion later from 46 to 48, and he correctly insisted on man's having an XX/XY system.[28]

New techniques were needed to definitively solve the problem:

1. Using cells in culture

2. Pretreating cells in a hypotonic solution, which swells them and spreads the chromosomes

3. Arresting mitosis in metaphase by a solution of colchicine

4. Squashing the preparation on the slide forcing the chromosomes into a single plane

5. Cutting up a photomicrograph and arranging the result into an indisputable karyogram.

It took until the mid-1950s for it to become generally accepted that the human karyotype include only 46 chromosomes. Considering the techniques of Winiwarter and Painter, their results were quite remarkable.[29] [30] Chimpanzees (the closest living relatives to modern humans) have 48 chromosomes.

Chromosomal aberrations

Chromosomal aberrations are disruptions in the normal chromosomal content of a cell, and are a major cause of genetic conditions in humans, such as Down syndrome. Some chromosome abnormalities do not cause disease in carriers, such as translocations, or chromosomal inversions, although they may lead to a higher chance of birthing a child with a chromosome disorder. Abnormal numbers of chromosomes or chromosome sets, aneuploidy, may be lethal or give rise to genetic disorders. Genetic counseling is offered for families that may carry a chromosome rearrangement.

The gain or loss of DNA from chromosomes can lead to a variety of genetic disorders. Human examples include:

- Cri du chat, which is caused by the deletion of part of the short arm of chromosome 5. "Cri du chat" means "cry of the cat" in French, and the condition was so-named because affected babies make high-pitched cries that sound like those of a cat. Affected individuals have wide-set eyes, a small head and jaw, and are moderately to severely mentally retarded and very short.

- Wolf-Hirschhorn syndrome, which is caused by partial deletion of the short arm of chromosome 4. It is characterized by severe growth retardation and severe to profound mental retardation.

- Down syndrome, usually is caused by an extra copy of chromosome 21 (trisomy 21). Characteristics include decreased muscle tone, stockier build, asymmetrical skull, slanting eyes and mild to moderate mental retardation.[31]

- Edwards syndrome, which is the second-most-common trisomy; Down syndrome is the most common. It is a trisomy of chromosome 18. Symptoms include mental and motor retardation and numerous congenital anomalies causing serious health problems. Ninety percent die in infancy; however, those that live past their first birthday usually are quite healthy thereafter. They have a characteristic clenched hands and overlapping fingers.

- Patau Syndrome, also called D-Syndrome or trisomy-13. Symptoms are somewhat similar to those of trisomy-18, but they do not have the characteristic hand shape.

- Idic15, abbreviation for Isodicentric 15 on chromosome 15; also called the following names due to various researches, but they all mean the same; IDIC(15), Inverted duplication 15, extra Marker, Inv dup 15, partial tetrasomy 15

- Jacobsen syndrome, also called the terminal 11q deletion disorder.[32] This is a very rare disorder. Those affected have normal intelligence or mild mental retardation, with poor expressive language skills. Most have a bleeding disorder called Paris-Trousseau syndrome.

The three major single chromosome mutations; deletion (1), duplication (2) and inversion (3).

The two major two-chromosome mutations; insertion (1) and translocation (2).

In Down syndrome, there are three copies of chromosome 21
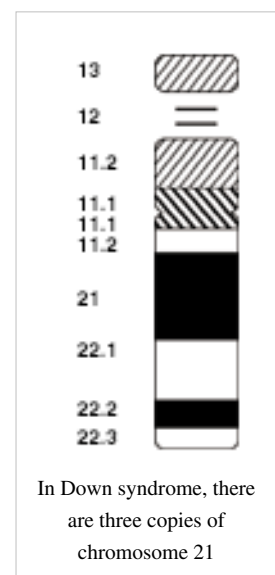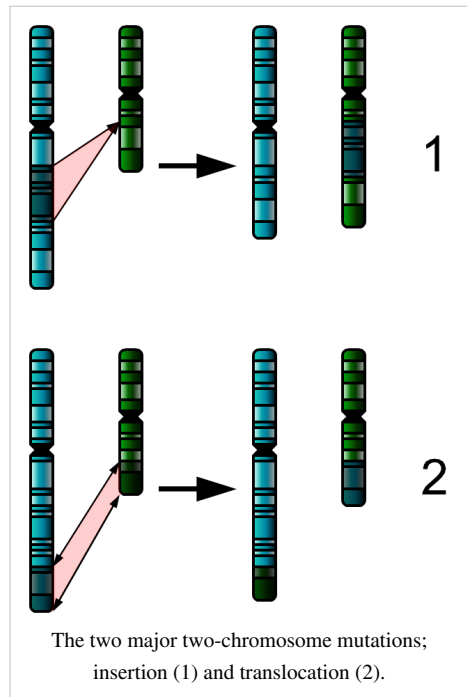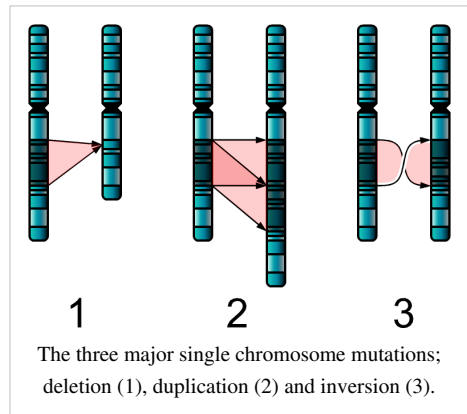
- Klinefelter's syndrome (XXY). Men with Klinefelter syndrome are usually sterile, and tend to have longer arms and legs and to be taller than their peers. Boys with the syndrome are often shy and quiet, and have a higher incidence of speech delay and dyslexia. During puberty, without testosterone treatment, some of them may develop gynecomastia.
- Turner syndrome (X instead of XX or XY). In Turner syndrome, female sexual characteristics are present but underdeveloped. People with Turner syndrome often have a short stature, low hairline, abnormal eye features and bone development and a "caved-in" appearance to the chest.
- XYY syndrome. XYY boys are usually taller than their siblings. Like XXY boys and XXX girls, they are somewhat more likely to have learning difficulties.
- Triple-X syndrome (XXX). XXX girls tend to be tall and thin. They have a higher incidence of dyslexia.
- Small supernumerary marker chromosome. This means there is an extra, abnormal chromosome. Features depend on the origin of the extra genetic material. Cat-eye syndrome and isodicentric chromosome 15 syndrome (or Idic15) are both caused by a supernumerary marker chromosome, as is Pallister-Killian syndrome.

Chromosomal mutations produce changes in whole chromosomes (more than one gene) or in the number of chromosomes present.

- Deletion – loss of part of a chromosome
- Duplication – extra copies of a part of a chromosome
- Inversion – reverse the direction of a part of a chromosome
- Translocation – part of a chromosome breaks off and attaches to another chromosome

Most mutations are neutral – have little or no effect. Chromosomal aberrations are the changes in the structure of chromosomes. It has a great role in evolution. A detailed graphical display of all human chromosomes and the diseases annotated at the correct spot may be found at[33] .

Human chromosomes

Chromosomes can be divided into two types--autosomes, and sex chromosomes. Certain genetic traits are linked to your sex, and are passed on through the sex chromosomes. The autosomes contain the rest of the genetic hereditary information. All act in the same way during cell division. Human cells have 23 pairs of large linear nuclear chromosomes, (22 pairs of autosomes and one pair of sex chromosomes) giving a total of 46 per cell. In addition to these, human cells have many hundreds of copies of the mitochondrial genome. Sequencing of the human genome has provided a great deal of information about each of the chromosomes. Below is a table compiling statistics for the chromosomes, based on the Sanger Institute's human genome information in the Vertebrate Genome Annotation (VEGA) database.[34] Number of genes is an estimate as it is in part based on gene predictions. Total chromosome length is an estimate as well, based on the estimated size of unsequenced heterochromatin regions.
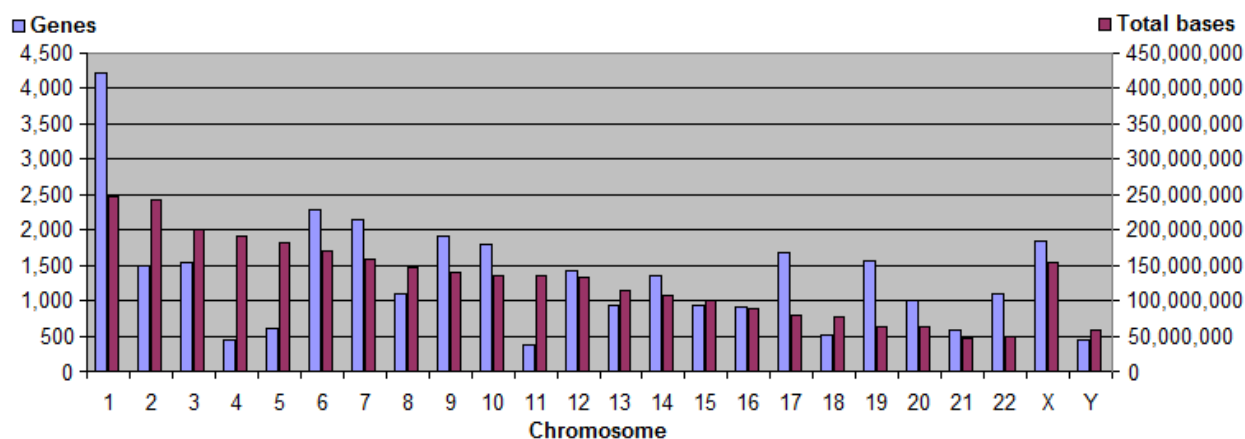
Chromosome	Genes	Total bases	Sequenced bases[35]
1	4,220	247,199,719	224,999,719
2	1,491	242,751,149	237,712,649
3	1,550	199,446,827	194,704,827
4	446	191,263,063	187,297,063
5	609	180,837,866	177,702,766
6	2,281	170,896,993	167,273,993
7	2,135	158,821,424	154,952,424
8	1,106	146,274,826	142,612,826
9	1,920	140,442,298	120,312,298
10	1,793	135,374,737	131,624,737
11	379	134,452,384	131,130,853
12	1,430	132,289,534	130,303,534
13	924	114,127,980	95,559,980
14	1,347	106,360,585	88,290,585
15	921	100,338,915	81,341,915
16	909	88,822,254	78,884,754
17	1,672	78,654,742	77,800,220
18	519	76,117,153	74,656,155
19	1,555	63,806,651	55,785,651
20	1,008	62,435,965	59,505,254
21	578	46,944,323	34,171,998
22	1,092	49,528,953	34,893,953
X (sex chromosome)	1,846	154,913,754	151,058,754
Y (sex chromosome)	454	57,741,652	25,121,652
Total	**32,185**	**3,079,843,747**	**2,857,698,560**

See also

- Locus (explains gene location nomenclature)
- Sex-determination system
  - XY sex-determination system
    - X chromosome
      - X-inactivation
    - Y chromosome
      - Y-chromosomal Adam
      - Y-chromosomal Aaron
- Genetic genealogy
  - Genealogical DNA test
- Genetic deletion

- List of number of chromosomes of various organisms
- For information about chromosomes in genetic algorithms, see chromosome (genetic algorithm)

External links

- An Introduction to DNA and Chromosomes [167] from HOPES: Huntington's Outreach Project for Education at Stanford
- Chromosome Abnormalities at AtlasGeneticsOncology [36]
- What Can Our Chromosomes Tell Us? [37], from the University of Utah's Genetic Science Learning Center
- Try making a karyotype yourself [38], from the University of Utah's Genetic Science Learning Center
- Kimballs Chromosome pages [39]
- Chromosome News from Genome News Network [40]
- Eurochromnet [41], European network for Rare Chromosome Disorders on the Internet
- http://www.ensembl.org Ensembl project, presenting chromosomes, their genes and syntenic loci graphically via the web
- Genographic Project [42]
- Home reference on Chromosomes [43] from the U.S. National Library of Medicine
- Visualisation of human chromosomes [44] and comparison to other species
- Unique - The Rare Chromosome Disorder Support Group [45] Support for people with rare chromosome disorders

Chromosome numbers (2n) in some animals

Species	#	Species	#
Common fruit fly	8	Guinea Pig[46]	64
Guppy (*poecilia reticulata*)[47]	23	Garden snail[48]	54
Earthworm *Octodrilus complanatus*[49]	36	Tibetan fox	36
Domestic cat[50]	38	Domestic pig	38
Laboratory mouse[51] [52]	40	Laboratory rat[52]	42
Rabbit (*Oryctolagus cuniculus*)[53]	44	Syrian hamster[51]	44
Hares[54] [55]	48	Human[56]	46
Gorillas, Chimpanzees[56]	48	Domestic sheep	54
Elephants[57]	56	Cow	60
Donkey	62	Horse	64
Dog[58]	78	Kingfisher[59]	132
Goldfish[60]	100-104	Silkworm[61]	56

References

[1] Paux E, Sourdille P, Salse J, *et al.* (2008). "A Physical Map of the 1-Gigabase Bread Wheat Chromosome 3B". *Science* **322** (5898): 101–104. doi: 10.1126/science.1161847 (http://dx.doi.org/10.1126/science.1161847). PMID 18832645 (http://www.ncbi.nlm.nih.gov/pubmed/18832645).

[2] Haeckel E. 1866. *Generelle Morphologie der Organismen: Allgemeine Gründzuge der organischen Formen-Wissenschaft.* 2 vols, Reimer, Berlin.

[3] Mayr E. 1982. *The growth of biological thought.* Harvard. p749

[4] Thanbichler M, Shapiro L (2006). "Chromosome organization and segregation in bacteria". *J. Struct. Biol.* **156** (2): 292–303. doi: 10.1016/j.jsb.2006.05.007 (http://dx.doi.org/10.1016/j.jsb.2006.05.007). PMID 16860572 (http://www.ncbi.nlm.nih.gov/pubmed/16860572).

[5] Nakabachi A, Yamashita A, Toh H, Ishikawa H, Dunbar H, Moran N, Hattori M (2006). "The 160-kilobase genome of the bacterial endosymbiont Carsonella". *Science* **314** (5797): 267. doi: 10.1126/science.1134196 (http://dx.doi.org/10.1126/science.1134196). PMID 17038615 (http://www.ncbi.nlm.nih.gov/pubmed/17038615).

[6] Pradella S, Hans A, Spröer C, Reichenbach H, Gerth K, Beyer S (2002). "Characterisation, genome size and genetic manipulation of the myxobacterium Sorangium cellulosum So ce56". *Arch Microbiol* **178** (6): 484–92. doi: 10.1007/s00203-002-0479-2 (http://dx.doi.org/10.1007/s00203-002-0479-2). PMID 12420170 (http://www.ncbi.nlm.nih.gov/pubmed/12420170).

[7] Hinnebusch J, Tilly K (1993). "Linear plasmids and chromosomes in bacteria". *Mol Microbiol* **10** (5): 917–22. doi: 10.1111/j.1365-2958.1993.tb00963.x (http://dx.doi.org/10.1111/j.1365-2958.1993.tb00963.x). PMID 7934868 (http://www.ncbi.nlm.nih.gov/pubmed/7934868).

[8] Kelman LM, Kelman Z (2004). "Multiple origins of replication in archaea". *Trends Microbiol.* **12** (9): 399–401. doi: 10.1016/j.tim.2004.07.001 (http://dx.doi.org/10.1016/j.tim.2004.07.001). PMID 15337158 (http://www.ncbi.nlm.nih.gov/pubmed/15337158).

[9] Thanbichler M, Wang SC, Shapiro L (2005). "The bacterial nucleoid: a highly organized and dynamic structure". *J. Cell. Biochem.* **96** (3): 506–21. doi: 10.1002/jcb.20519 (http://dx.doi.org/10.1002/jcb.20519). PMID 15988757 (http://www.ncbi.nlm.nih.gov/pubmed/15988757).

[10] Sandman K, Pereira SL, Reeve JN (1998). "Diversity of prokaryotic chromosomal proteins and the origin of the nucleosome". *Cell. Mol. Life Sci.* **54** (12): 1350–64. doi: 10.1007/s000180050259 (http://dx.doi.org/10.1007/s000180050259). PMID 9893710 (http://www.ncbi.nlm.nih.gov/pubmed/9893710).

[11] Sandman K, Reeve JN (2000). "Structure and functional relationships of archaeal and eukaryal histones and nucleosomes". *Arch. Microbiol.* **173** (3): 165–9. doi: 10.1007/s002039900122 (http://dx.doi.org/10.1007/s002039900122). PMID 10763747 (http://www.ncbi.nlm.nih.gov/pubmed/10763747).

[12] Pereira SL, Grayling RA, Lurz R, Reeve JN (1997). "Archaeal nucleosomes" (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=9356501). *Proc. Natl. Acad. Sci. U.S.A* **94** (23): 12633–7. doi: 10.1073/pnas.94.23.12633 (http://dx.doi.org/10.1073/pnas.94.23.12633). PMID 9356501 (http://www.ncbi.nlm.nih.gov/pubmed/9356501). PMC 25063 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=25063). .

[13] Armstrong SJ, Jones GH (January 2003). "Meiotic cytology and chromosome behaviour in wild-type Arabidopsis thaliana" (http://jexbot.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=12456750). *J. Exp. Bot.* **54** (380): 1–10. doi: 10.1093/jxb/54.380.1 (http://dx.doi.org/10.1093/jxb/54.380.1). PMID 12456750 (http://www.ncbi.nlm.nih.gov/pubmed/12456750). .

[14] Gill BS, Kimber G (April 1974). "The Giemsa C-banded karyotype of rye" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=388202). *Proc. Natl. Acad. Sci. U.S.A.* **71** (4): 1247–9. doi: 10.1073/pnas.71.4.1247 (http://dx.doi.org/10.1073/pnas.71.4.1247). PMID 4133848 (http://www.ncbi.nlm.nih.gov/pubmed/4133848).

[15] Kato A, Lamb JC, Birchler JA (September 2004). "Chromosome painting using repetitive DNA sequences as probes for somatic chromosome identification in maize" (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=15342909). *Proc. Natl. Acad. Sci. U.S.A.* **101** (37): 13554–9. doi: 10.1073/pnas.0403659101 (http://dx.doi.org/10.1073/pnas.0403659101). PMID 15342909 (http://www.ncbi.nlm.nih.gov/pubmed/15342909). PMC 518793 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=518793). .

[16] Dubcovsky J, Luo MC, Zhong GY, *et al.* (1996). "Genetic map of diploid wheat, Triticum monococcum L., and its comparison with maps of Hordeum vulgare L" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1207354). *Genetics* **143** (2): 983–99. PMID 8725244 (http://www.ncbi.nlm.nih.gov/pubmed/8725244).

[17] Kenton A, Parokonny AS, Gleba YY, Bennett MD (August 1993). "Characterization of the Nicotiana tabacum L. genome by molecular cytogenetics". *Mol. Gen. Genet.* **240** (2): 159–69. doi: 10.1007/BF00277053 (http://dx.doi.org/10.1007/BF00277053). PMID 8355650 (http://www.ncbi.nlm.nih.gov/pubmed/8355650).

[18] Leitch IJ, Soltis DE, Soltis PS, Bennett MD (2005). "Evolution of DNA amounts across land plants (embryophyta)" (http://aob.oxfordjournals.org/cgi/content/full/95/1/207). *Ann. Bot.* **95** (1): 207–17. doi: 10.1093/aob/mci014 (http://dx.doi.org/10.1093/aob/mci014). PMID 15596468 (http://www.ncbi.nlm.nih.gov/pubmed/15596468). .

[19] Itoh, Masahiro; Tatsuro Ikeuchi, Hachiro Shimba, Michiko Mori, Motomichi Sasaki, Sajiro Makino (1969). "A COMPARATIVE KARYOTYPE STUDY IN FOURTEEN SPECIES OF BIRDS" (http://www.journalarchive.jst.go.jp/english/jnlabstract_en.php?cdjournal=ggs1921&cdvol=44&noissue=3&startpage=163). *The Japanese journal of genetics* **44** (3): 163–170. doi: 10.1266/jjg.44.163

(http://dx.doi.org/10.1266/jjg.44.163). ISSN 1880-5787 (http://worldcat.org/issn/1880-5787). . Retrieved 2009-10-14.

[20] Smith J, Burt DW (1998). "Parameters of the chicken genome (Gallus gallus)". *Anim. Genet.* **29** (4): 290–4. doi: 10.1046/j.1365-2052.1998.00334.x (http://dx.doi.org/10.1046/j.1365-2052.1998.00334.x). PMID 9745667 (http://www.ncbi.nlm. nih.gov/pubmed/9745667).

[21] Sakamura, T. (1918), *Kurze Mitteilung uber die Chromosomenzahlen und die Verwandtschaftsverhaltnisse der Triticum-Arten*. Bot. Mag., 32: 151-154.

[22] Charlebois R.L. (ed) 1999. *Organization of the prokaryote genome*. ASM Press, Washington DC.

[23] Komaki K, Ishikawa H (March 2000). "Genomic copy number of intracellular bacterial symbionts of aphids varies in response to developmental stage and morph of their host". *Insect Biochem. Mol. Biol.* **30** (3): 253–8. doi: 10.1016/S0965-1748(99)00125-3 (http://dx. doi.org/10.1016/S0965-1748(99)00125-3). PMID 10732993 (http://www.ncbi.nlm.nih.gov/pubmed/10732993).

[24] Mendell JE, Clements KD, Choat JH, Angert ER (May 2008). "Extreme polyploidy in a large bacterium" (http://www.pnas.org/cgi/ pmidlookup?view=long&pmid=18445653). *Proc. Natl. Acad. Sci. U.S.A.* **105** (18): 6730–4. doi: 10.1073/pnas.0707522105 (http://dx.doi. org/10.1073/pnas.0707522105). PMID 18445653 (http://www.ncbi.nlm.nih.gov/pubmed/18445653). PMC 2373351 (http://www. pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2373351). .

[25] White, M. J. D. (1973). *The chromosomes* (6th ed.). London: Chapman and Hall, distributed by Halsted Press, New York. pp. 28. ISBN 0-412-11930-7.

[26] von Winiwarter H (1912). "Études sur la spermatogenese humaine". *Arch. Biologie* **27** (93): 147–9.

[27] Painter TS (1922). "The spermatogenesis of man". *Anat. Res.* **23**: 129.

[28] Painter TS (1923). "Studies in mammalian spermatogenesis II. The spermatogenesis of man". *J. Exp. Zoology* **37**: 291–336. doi: 10.1002/jez.1400370303 (http://dx.doi.org/10.1002/jez.1400370303).

[29] Tjio JH, Levan A (1956). "The chromosome number of man". *Hereditas* **42**: 1–6.

[30] Hsu T.C. *Human and mammalian cytogenetics: a historical perspective*. Springer-Verlag, N.Y. p10: "It's amazing that he [Painter] even came close!"

[31] Miller, Kenneth R. (2000). "9-3". *Biology* (5th ed.). Upper Saddle River, New Jersey: Prentice Hall. pp. 194–5. ISBN 0-13-436265-9.

[32] European Chromosome 11 Network (http://www.11q.org)

[33] Exploring Genes & Genetic Disorders (http://www.ornl.gov/hgmis/posters/chromosome/)

[34] http://vega.sanger.ac.uk/Homo_sapiens/index.html All data in this table was derived from this database, Nov 11, 2008.

[35] Sequenced percentages are based on fraction of euchromatin portion, as the Human Genome Project goals called for determination of only the euchromatic portion of the genome. Telomeres, centromeres, and other heterochromatic regions have been left undetermined, as have a small number of unclonable gaps. See http://www.ncbi.nlm.nih.gov/genome/seq/for more information on the Human Genome Project.

[36] http://atlasgeneticsoncology.org/Educ/PolyMecaEng.html

[37] http://learn.genetics.utah.edu/content/begin/traits/predictdisorder/

[38] http://learn.genetics.utah.edu/content/begin/traits/karyotype/index.html

[39] http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/C/Chromosomes.html

[40] http://www.genomenewsnetwork.org/categories/index/genome/chromosomes.php

[41] http://www.chromosomehelpstation.com/eurochromnet.htm

[42] https://www3.nationalgeographic.com/genographic/index.html

[43] http://ghr.nlm.nih.gov/ghr/chromosomes

[44] http://www.dna-rainbow.org

[45] http://www.rarechromo.org

[46] Umeko Semba, Yasuko Umeda, Yoko Shibuya, Hiroaki Okabe, Sumio Tanase and Tetsuro Yamamoto (2004). "Primary structures of guinea pig high- and low-molecular-weight kininogens" (http://www.sciencedirect.com/science/article/B6W7N-4CX6PRC-1/2/ 97487fdf611a04e3c88690da9e6d853b). *International Immunopharmacology* **4** (10-11): 1391–1400. doi: 10.1016/j.intimp.2004.06.003 (http://dx.doi.org/10.1016/j.intimp.2004.06.003). PMID 15313436 (http://www.ncbi.nlm.nih.gov/pubmed/15313436). .

[47] "The Genetics of the Popular Aquarium Pet - Guppy Fish" (http://fancyguppy.webs.com/genetics.htm). . Retrieved 2009-12-06.

[48] Vitturi R, Libertini A, Sineo L, *et al.* (2005). "Cytogenetics of the land snails Cantareus aspersus and C. mazzullii (Mollusca: Gastropoda: Pulmonata)". *Micron* **36** (4): 351–7. doi: 10.1016/j.micron.2004.12.010 (http://dx.doi.org/10.1016/j.micron.2004.12.010). PMID 15857774 (http://www.ncbi.nlm.nih.gov/pubmed/15857774).

[49] Vitturi R, Colomba MS, Pirrone AM, Mandrioli M (2002). "rDNA (18S-28S and 5S) colocalization and linkage between ribosomal genes and (TTAGGG)(n) telomeric sequence in the earthworm, Octodrilus complanatus (Annelida: Oligochaeta: Lumbricidae), revealed by single- and double-color FISH" (http://jhered.oxfordjournals.org/cgi/content/full/93/4/279). *J. Hered.* **93** (4): 279–82. doi: 10.1093/jhered/93.4.279 (http://dx.doi.org/10.1093/jhered/93.4.279). PMID 12407215 (http://www.ncbi.nlm.nih.gov/pubmed/ 12407215). .

[50] Nie W, Wang J, O'Brien PC, *et al.* (2002). "The genome phylogeny of domestic cat, red panda and five mustelid species revealed by comparative chromosome painting and G-banding". *Chromosome Res.* **10** (3): 209–22. doi: 10.1023/A:1015292005631 (http://dx.doi.org/ 10.1023/A:1015292005631). PMID 12067210 (http://www.ncbi.nlm.nih.gov/pubmed/12067210).

[51] Romanenko, Svetlana A; Polina L Perelman, Natalya A Serdukova, Vladimir A Trifonov, Larisa S Biltueva, Jinhuan Wang, Tangliang Li, Wenhui Nie, Patricia C M O'Brien, Vitaly T Volobouev, Roscoe Stanyon, Malcolm A Ferguson-Smith, Fengtang Yang, Alexander S Graphodatsky (2006-12). "Reciprocal chromosome painting between three laboratory rodent species" (http://www.ncbi.nlm.nih.gov/

pubmed/17143584). *Mammalian Genome: Official Journal of the International Mammalian Genome Society* **17** (12): 1183–1192. doi: 10.1007/s00335-006-0081-z (http://dx.doi.org/10.1007/s00335-006-0081-z). ISSN 0938-8990 (http://worldcat.org/issn/0938-8990). . Retrieved 2009-10-14.

[52] A COMPARISON OF THE CHROMOSOMES OF THE RAT AND MOUSE WITH REFERENCE TO THE QUESTION OF CHROMOSOME HOMOLOGY IN MAMMALS (http://www.esp.org/foundations/genetics/classical/holdings/Genetics/Genetics-1928-13-2-180.pdf)

[53] Hayes, H.; C. Rogel-Gaillard, C. Zijlstra, N.A. de Haan, C. Urien, N. Bourgeaux, M. Bertaud, A.A. Bosma (2002). "Establishment of an R-banded rabbit karyotype nomenclature by FISH localization of 23 chromosome-specific genes on both G- and R-banded chromosomes" (http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=CGR98199). *Cytogenetic and Genome Research* **98** (2-3): 199–205. doi: 10.1159/000069807 (http://dx.doi.org/10.1159/000069807). ISSN 1424-859X (http://worldcat.org/issn/1424-859X). PMID 12698004 (http://www.ncbi.nlm.nih.gov/pubmed/12698004). . Retrieved 2009-10-14.

[54] T.J. Robinson, F. Yang, W.R. Harrison (2002). "Chromosome painting refines the history of genome evolution in hares and rabbits (order Lagomorpha)" (http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstract&ArtikelNr=63034&Ausgabe=228416&ProduktNr=224037). *Cytogenic and Genetic Research* **96** (1-4): 223–227. doi: 10.1159/000063034 (http://dx.doi.org/10.1159/000063034). PMID 12438803 (http://www.ncbi.nlm.nih.gov/pubmed/12438803). .

[55] "Rabbits, Hares and Pikas. Status Survey and Conservation Action Plan" (http://wildlife1.wildlifeinformation.org/s/00Ref/BooksContents/b605.htm). pp. 61–94. .

[56] De Grouchy J (1987). "Chromosome phylogenies of man, great apes, and Old World monkeys". *Genetica* **73** (1-2): 37–52. PMID 3333352 (http://www.ncbi.nlm.nih.gov/pubmed/3333352).

[57] Houck ML, Kumamoto AT, Gallagher DS, Benirschke K (2001). "Comparative cytogenetics of the African elephant (Loxodonta africana) and Asiatic elephant (Elephas maximus)". *Cytogenet. Cell Genet.* **93** (3-4): 249–52. doi: 10.1159/000056992 (http://dx.doi.org/10.1159/000056992). PMID 11528120 (http://www.ncbi.nlm.nih.gov/pubmed/11528120).

[58] Wayne RK, Ostrander EA (1999). "Origin, genetic diversity, and genome structure of the domestic dog". *Bioessays* **21** (3): 247–57. doi:10.1002/(SICI)1521-1878(199903)21:3 (inactive 2009-03-11) . PMID 10333734 (http://www.ncbi.nlm.nih.gov/pubmed/10333734).

[59] Burt DW (2002). "Origin and evolution of avian microchromosomes". *Cytogenet. Genome Res.* **96** (1-4): 97–112. doi: 10.1159/000063018 (http://dx.doi.org/10.1159/000063018). PMID 12438785 (http://www.ncbi.nlm.nih.gov/pubmed/12438785).

[60] Ciudad J, Cid E, Velasco A, Lara JM, Aijón J, Orfao A (2002). "Flow cytometry measurement of the DNA contents of G0/G1 diploid cells from three different teleost fish species". *Cytometry* **48** (1): 20–5. doi: 10.1002/cyto.10100 (http://dx.doi.org/10.1002/cyto.10100). PMID 12116377 (http://www.ncbi.nlm.nih.gov/pubmed/12116377).

[61] Yasukochi Y, Ashakumary LA, Baba K, Yoshido A, Sahara K (2006). "A second-generation integrated map of the silkworm reveals synteny and conserved gene order between lepidopteran insects" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1526672). *Genetics* **173** (3): 1319–28. doi: 10.1534/genetics.106.055541 (http://dx.doi.org/10.1534/genetics.106.055541). PMID 16547103 (http://www.ncbi.nlm.nih.gov/pubmed/16547103).

Telomere

A **telomere** is a region of repetitive DNA at the end of a chromosome, which protects the end of the chromosome from deterioration. Its name is derived from the Greek nouns telos (τέλος) "end" and meros (μέρος, root: μερ-) "part".

Russian theorist Alexei Olovnikov was the first to recognize (1971) the problem of how chromosomes could replicate right to the tip, as such was impossible with replication in a 5' to 3' direction. To solve this and to accommodate Leonard Hayflick's idea of limited somatic cell division, Olovnikov suggested that DNA sequences would be lost in every replicative phase until they reached a critical level, at which point cell division would stop.[1] [2]
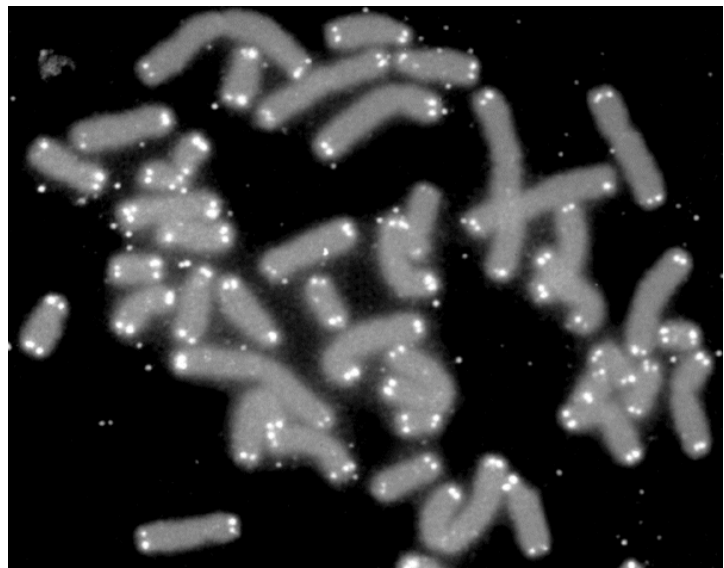
Human chromosomes (grey) capped by telomeres (white)

During cell division, the enzymes that duplicate the chromosome and its DNA cannot continue their duplication all the way to the end of the chromosome. If cells divided without telomeres, they would lose the ends of their chromosomes, and the necessary information they contain. (In 1972, James Watson named this phenomenon the "end replication problem".) The telomeres are disposable buffers blocking the ends of the chromosomes and are consumed during cell division and replenished by an enzyme, the telomerase reverse transcriptase.

They have been likened to the aglets (tips) on the ends of shoelaces that keep them from fraying.[3]

In 1975–1977, Blackburn, working as a postdoctoral fellow at Yale University with Joseph Gall, discovered the unusual nature of telomeres, with their simple repeated DNA sequences composing chromosome ends. Their work was published in 1978. The telomere shortening mechanism normally limits cells to a fixed number of divisions, and animal studies suggest that this is responsible for aging on the cellular level and sets a limit on lifespans. Telomeres protect a cell's chromosomes from fusing with each other or rearranging—abnormalities which can lead to cancer—and so cells are normally destroyed when their telomeres are consumed. Most cancers are the result of "immortal" cells which have ways of evading this programmed destruction.[4]

Elizabeth Blackburn, Carol Greider, and Jack Szostak were awarded the 2009 Nobel Prize in Physiology or Medicine for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase.[5]

Nature and function of telomeres

Structure and function

Telomeres are repetitive DNA sequences located at the termini of linear chromosomes of most eukaryotic organisms, and a few prokaryotes. Telomeres compensate for incomplete semi-conservative DNA replication at chromosomal ends. The protection against homologous recombination (HR) and non-homologous end joining (NHEJ) constitutes the essential "capping" role of telomeres that distinguishes them from DNA double-strand breaks (DSBs) (Lundblad, 2000; Ferreira *et al.*, 2004).
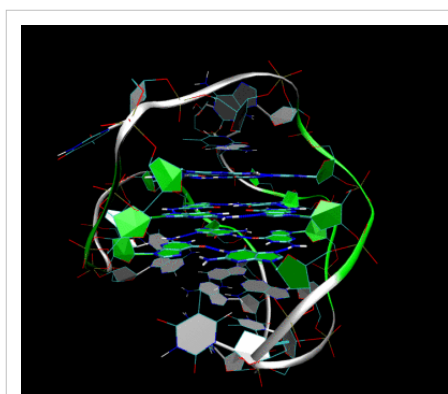
Three-dimensional molecular structure of a telomere.

In most prokaryotes, chromosomes are circular and thus do not have ends to suffer premature replication termination. A small fraction of bacterial chromosomes (such as those in Streptomyces and Borrelia) are linear and possess telomeres, which are very different from those of the eukaryotic chromosomes in structure and functions. The known structures of bacterial telomeres take the form of proteins bound to the ends of linear chromosomes, or hairpin loops of single-stranded DNA at the ends of the linear chromosomes.[6]

In most multicellular eukaryotic organisms, telomerase is active only in germ cells, stem cells and certain white blood cells. There are theories that the steady shortening of telomeres with each replication in somatic (body) cells may have a role in senescence and in the prevention of cancer. This is because the telomeres act as a sort of time-delay "fuse", eventually running out after a certain number of cell divisions and resulting in the eventual loss of vital genetic information from the cell's chromosome with future divisions.

Telomere length varies greatly between species, from approximately 300 to 600 base pairs in yeast (Shampay *et al.*, 1984) to many kilobases in humans, and usually is composed of arrays of guanine-rich, six-to-eight base-pair-long repeats. Eukaryotic telomeres normally terminate with 3′ single-stranded-DNA overhang which is essential for telomere maintenance and capping. Multiple proteins binding single- and double-stranded telomere DNA have been identified (Blackburn, 2001; Smogorzewska and de Lange, 2004; Cech, 2004; De Lange *et al.*, 2005; Kota and Runge, 1999). These function in both telomere maintenance and capping.

Telomere shortening in humans can induce replicative senescence which blocks cell division. This mechanism appears to prevent genomic instability and development of cancer in human aged cells by limiting the number of cell divisions. Malignant cells which bypass this arrest become immortalized by telomere extension mostly due to the activation of telomerase, the reverse transcriptase enzyme responsible for synthesis of telomeres. However, 5−10% of human cancers activate the Alternative Lengthening of Telomeres (ALT) pathway which relies on recombination-mediated elongation.

Human telomeres, cancer and ALT

Human somatic cells lacking telomerase gradually lose telomeric sequences as a result of incomplete replication (Counter *et al.*, 1992). As human telomeres grow shorter, eventually cells reach the limit of their replicative capacity and progress into senescence. Senescence involves p53 and pRb pathways and leads to the arrest of cell proliferation (Campisi, 2005). It is thought that senescence plays an important role in suppression of emergence of cancer. However, further cell proliferation can be achieved by inactivation of p53 and pRb pathways. Cells entering proliferation after inactivation of p53 and pRb pathways undergo crisis. Crisis is characterized by gross chromosomal rearrangements and genome instability, and almost all cells die. Rare cells emerge from crisis immortalized through telomere elongation by either activated telomerase or ALT (Colgina and Reddel, 1999; Reddel and Bryan, 2003). The first description of an ALT cell line demonstrated that the telomeres were highly heterogeneous in length and predicted a mechanism involving recombination (Murnane et al., 1994). Subsequent studies have confirmed a role for recombination in telomere maintenance by ALT (Dunham et al., 2000), however, the exact mechanism of this pathway is yet to be determined. ALT cells produce abundant t-circles, possible products of intratelomeric recombination and t-loop resolution (Cesare and Griffith, 2004; Wang *et al.*, 2004).

Telomerase is a "ribonucleoprotein complex" composed of a protein component and an RNA primer sequence which acts to protect the terminal ends of chromosomes. The actions of telomerase are necessary because, during replication, DNA polymerase can only synthesize DNA in a 5' to 3' direction and can only do so by adding polynucleotides to an RNA primer that has already been placed at various points along the length of the DNA. These

RNA strands must later be replaced with DNA. This replacement of the RNA primers is not a problem at origins of replication within the chromosome because DNA polymerase can use a previous stretch of DNA 5' to the RNA template as a template to backfill the sequence where the RNA primer was; at the terminal end of the chromosome, however, DNA polymerase cannot replace the RNA primer because there is no position 5' of the RNA primer where another primer can be placed nor is there DNA upstream that can be used as a primer so that DNA polymerase can replace the RNA primer. Without telomeres at the end of DNA, this genetic sequence at the end of the chromosome would be deleted and the chromosome would grow shorter and shorter in subsequent replications. The telomere prevents this problem by employing a different mechanism to synthesize DNA at this point, thereby preserving the sequence at the terminal of the chromosome. This prevents chromosomal fraying and prevents the ends of the chromosome from being processed as a double strand DNA break, which could lead to chromosome-to-chromosome telomere fusions. Telomeres are extended by telomerases, part of a protein subgroup of specialized reverse transcriptase enzymes known as TERT (**TE**lomerase **R**everse **T**ranscriptases) that are involved in synthesis of telomeres in humans and many other, but not all, organisms. However, because of DNA replication mechanisms, oxidative stress, and because TERT expression is very low in many types of human cells, the telomeres of these cells shrink a little bit every time a cell divides although in other cellular compartments which require extensive cell division, such as stem cells and certain white blood cells, TERT is expressed at higher levels and telomere shortening is partially or fully prevented.

In addition to its TERT protein component, telomerase also contains a piece of template RNA known as the TERC (**TE**lomerase **R**NA **C**omponent) or TR (**T**elomerase **R**NA). In humans, this TERC telomere sequence is a repeating string of TTAGGG, between 3 and 20 kilobases in length. There are an additional 100-300 kilobases of telomere-associated repeats between the telomere and the rest of the chromosome. Telomere sequences vary from species to species, but generally one strand is rich in G with fewer Cs. These G-rich sequences can form four-stranded structures (G-quadruplexes), with sets of four bases held in plane and then stacked on top of each other with either a sodium or potassium ion between the planar quadruplexes.

Structure of parallel quadruplexes that can be formed by human telomeric DNA. Image created from NDB UD0017 [7].
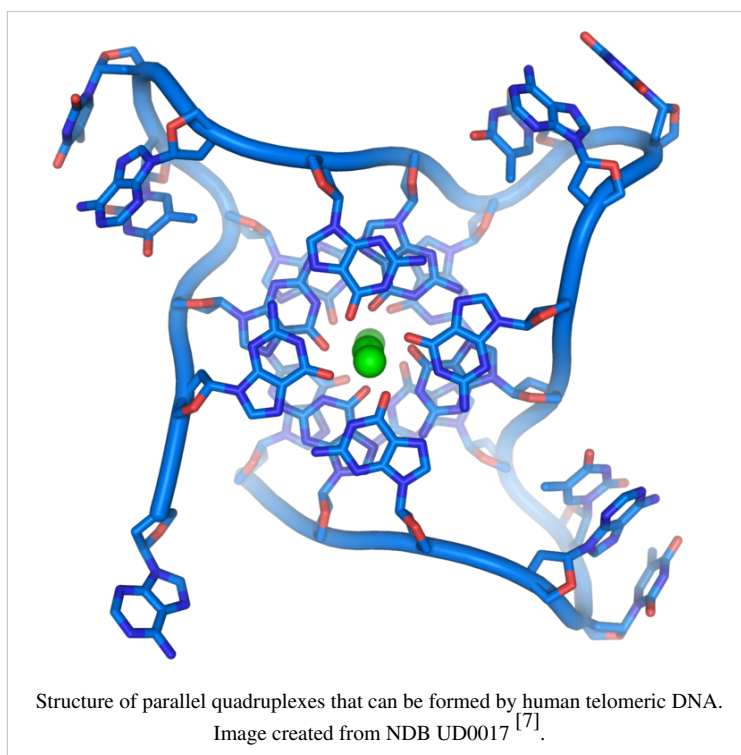
If telomeres become too short, they will potentially unfold from their presumed closed structure. It is thought that the cell detects this uncapping as DNA damage and then enters cellular senescence, growth arrest or apoptosis, depending on the cell's genetic background (p53 status). Uncapped telomeres also result in chromosomal fusions. Since this damage cannot be repaired in normal somatic cells, the cell may even go into apoptosis. Many aging-related diseases are linked to shortened telomeres. Organs deteriorate as more and more of their cells die off or enter cellular senescence.

At the very distal end of the telomere is a 300 bp single-stranded portion which forms the T-Loop. This loop is analogous to a 'knot' which stabilizes the telomere, preventing the telomere ends from being recognized as break points by the DNA repair machinery. Should non-homologous end joining occur at the telomeric ends, chromosomal fusion will result. The T-loop is held together by seven known proteins; most notably TRF1, TRF2, POT1, TIN1,

and TIN2, collectively referred to as the shelterin complex.

A study published in the May 3, 2005 issue of the American Heart Association journal *Circulation* found that weight gain and increased insulin resistance were correlated with greater telomere shortening over time.

Telomere shortening

Telomeres shorten in part because of the *end replication problem* that is exhibited during DNA replication in eukaryotes only. Because DNA replication does not begin at either end of the DNA strand, but starts in the center, and considering that all DNA polymerases that have been discovered move in the 5' to 3' direction, one finds a leading and a lagging strand on the DNA molecule being replicated.

On the leading strand, DNA polymerase can make a complementary DNA strand without any difficulty because it goes from 5' to 3'. However, there is a problem going in the other direction on the lagging strand. To counter this, short sequences of RNA acting as primers attach to the lagging strand a short distance ahead of where the initiation site was. The DNA polymerase can start replication at that point and go to

Lagging strand during DNA replication

the end of the initiation site. This causes the formation of Okazaki fragments. More RNA primers attach further on the DNA strand and DNA polymerase comes along and continues to make a new DNA strand.
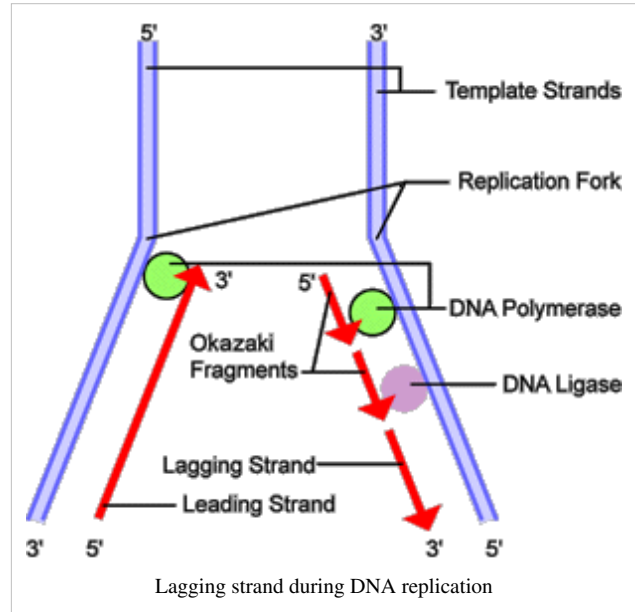
Eventually, the last RNA primer attaches, and DNA polymerase, RNA nuclease and DNA ligase come along to convert the RNA (of the primers) to DNA and to seal the gaps in between the Okazaki fragments. But in order to change RNA to DNA, there must be another DNA strand in front of the RNA primer. This happens at all the sites of the lagging strand, but it does not happen at the end where the last RNA primer is attached. Ultimately, that RNA is destroyed by enzymes that degrade any RNA left on the DNA. Thus, a section of the telomere is lost during each cycle of replication at the 5' end of the lagging strand.

However, in vitro studies (von Zglinicki et al. 1995, 2000) have shown that telomeres are highly susceptible to oxidative stress. Telomere shortening due to free radicals explains the difference between the estimated loss per division because of the end-replication problem (ca. 20 bp) and actual telomere shortening rates (50-100 bp), and has a greater absolute impact on telomere length than shortening caused by the end-replication problem.

Lengthening telomeres

The phenomenon of limited cellular division was first observed by Leonard Hayflick, and is now referred to as the Hayflick limit. Significant discoveries were made by the team led by Professor Elizabeth Blackburn at the University of California, San Francisco (UCSF).

Advocates of human life extension promote the idea of lengthening the telomeres in certain cells through temporary activation of telomerase (by drugs), or possibly permanently by gene therapy. They reason that this would extend human life. So far these ideas have not been proven in humans.

However, it has been hypothesized that there is a trade-off between cancerous tumor suppression and tissue repair capacity, in that lengthening telomeres might slow aging and in exchange increase vulnerability to cancer (Weinstein and Ciszek, 2002).

A study done with the nematode worm species *Caenorhabditis elegans* indicates that there is a correlation between lengthening telomeres and a longer lifespan. Two groups of worms were studied which differed in the amount of the protein HRP-1 their cells produced, resulting in telomere lengthening in the mutant worms. The worms with the longer telomeres lived 24 days on average, about 20 percent longer than the normal worms.[8]

Techniques to extend telomeres could be useful for tissue engineering, because they might permit healthy, noncancerous mammalian cells to be cultured in amounts large enough to be engineering materials for biomedical repairs.

However, there are several issues that still need to be cleared up. First, it is not even certain whether the relationship between telomeres and aging is causal. Changing telomere lengths are usually associated with changing speed of senescence. This telomere shortening, however, might be a consequence of, and not a reason for, aging.

That the role of telomeres is far from being understood is demonstrated by two recent studies on long-lived seabirds. In 2003, scientists observed that the telomeres of Leach's Storm-petrel (*Oceanodroma leucorhoa*) seem to lengthen with chronological age, the first observed instance of such behaviour of telomeres.[9] In 2006, Juola *et al.*[10] reported that in another unrelated, long-lived seabird species, the Great Frigatebird (*Fregata minor*), telomere length did decrease until at least c.40 years of age (i.e. probably over the entire lifespan), but the speed of decrease slowed down massively with increasing ages, and that rates of telomere length decrease varied strongly between individual birds. They concluded that in this species (and probably in frigatebirds and their relatives in general), telomere length could not be used to determine a bird's age sufficiently well. Thus, it seems that there is much more variation in the behavior of telomere length than initially believed.

The telomere length varies in cloned animals. Sometimes the clones end up with shorter telomeres since the DNA has already divided countless times. Occasionally, the telomeres in a clone's DNA are longer because they get "reprogrammed". The clone's new telomeres combine with the old ones, giving it abnormally long telomeres.

In 2008, UCLA and Sierra Sciences confirmed two different small molecule compounds that activated Telomerase. Sierra Sciences, a biotechnology company in Reno, NV, has discovered a small-molecule, drug-like compound that turns on the expression of telomerase in human cells. Their scientists are presently characterizing its mechanism of action.[11] While UCLA confirmed a small-molecule extract from a plant, that turns on the expression of telomerase in human cell.[12]

In 2008, Dr. Dean Ornish of the Preventive Medicine Research Institute (Sausalito, CA) and colleagues at the University of California at San Francisco conducted a study of 30 men with low-risk prostate cancer on the possible effects of lifestyle changes on telomeres. The findings of the study were published in The Lancet Oncology. The men were asked to make several lifestyle changes, including attending a three-day retreat; eating a diet low in refined sugars and rich in whole foods, fruits, and vegetables, with only 10 percent of calories derived from fat; and engaging in several other activities, such as moderate aerobic exercise, relaxation techniques and breathing exercises. Telomerase levels were measured at baseline, and again after three months, when researchers discovered that, in the 24 participants with sufficient data for analysis, telomerase in the blood had increased by 29 percent. The authors commented that "The implications of this study are not limited to men with prostate cancer. Comprehensive lifestyle changes may cause improvements in telomerase and telomeres that may be beneficial to the general population as well." In a cautionary note due to the limited nature of the pilot study, the authors indicated the link between lifestyle changes and increases in telomerase activity was reported as "significant association rather than inferring causation" until wider studies are completed.[13] [14]

Measurement of telomere length in the laboratory

Several techniques are currently employed to assess average telomere length in eukaryotic cells. The most widely used method is the Terminal Restriction Fragment (TRF) southern blot, which involves hybridization of a radioactive 32P-(TTAGGG)n oligonucleotide probe to Hinf / Rsa I digested genomic DNA embedded on a nylon membrane and subsequently exposed to autoradiographic film or phosphoimager screen. Another histochemical method, termed Q-FISH, involves fluorescent in situ hybridization (FISH). Q-FISH, however, requires significant amounts of genomic DNA (2-20 micrograms) and labor which renders its use limited in large epidemiological studies. Some of these impediments have been overcome with a Real-Time PCR assay for telomere length and Flow-FISH. RT-PCR assay involves determining the Telomere-to-Single Copy Gene (T/S)ratio, which is demonstrated to be proportional to the average telomere length in a cell. The Real-Time PCR assay has been since scaled up to high-throughput 384-well format use, making the assay feasible for use in large cohort studies. Flow-FISH is an adaptation of the Q-FISH telomere quantitation technique, which uses a flow cytometer to measure median fluorescence of a population of cells, thus reducing labor requirements and increasing reproducibility. Flow-FISH has been scaled up to the 96-well format.[15]

Another technique, referred to as single telomere elongation length analysis (STELA), was developed in 2003 by Duncan Baird. This technique is a PCR based technique. As a result, it is has a much higher resolution than previous telomere length analysis techniques. And because chromosome specific primers can be used, investigations can target specific telomere ends. This is something that is not possible with TRF analysis. However, due to this technique's being PCR-based, telomeres larger than 25Kb cannot be amplified and there is a bias towards shorter telomeres. This can be problematic when analysing ALT positive cell lines as these have very heterogeneous telomere lengths and can exhibit telomeres as large as 50Kb.

Telomere sequences

Some known telomere sequences

Group	Organism	Telomeric repeat (5' to 3' toward the end)
Vertebrates	Human, mouse, *Xenopus*	TTAGGG
Filamentous fungi	*Neurospora crassa*	TTAGGG
Slime moulds	*Physarum, Didymium*	TTAGGG
	Dictyostelium	AG(1-8)
Kinetoplastid protozoa	*Trypanosoma, Crithidia*	TTAGGG
Ciliate protozoa	*Tetrahymena, Glaucoma*	TTGGGG
	Paramecium	TTGGG(T/G)
	Oxytricha, Stylonychia, Euplotes	TTTTGGGG
Apicomplexan protozoa	*Plasmodium*	TTAGGG(T/C)
Higher plants	*Arabidopsis thaliana*	TTTAGGG
Green algae	*Chlamydomonas*	TTTTAGGG
Insects	*Bombyx mori*	TTAGG
Roundworms	*Ascaris lumbricoides*	TTAGGC
Fission yeasts	*Schizosaccharomyces pombe*	TTAC(A)(C)G(1-8)

Budding yeasts	*Saccharomyces cerevisiae*	TGTGGGTGTGGTG (from RNA template) or G(2-3)(TG)(1-6)T (consensus)
	Saccharomyces castellii	TCTGGGTG
	Candida glabrata	GGGGTCTGGGTGCTG
	Candida albicans	GGTGTACGGATGTCTAACTTCTT
	Candida tropicalis	GGTGTA[C/A]GGATGTCACGATCATT
	Candida maltosa	GGTGTACGGATGCAGACTCGCTT
	Candida guillermondii	GGTGTAC
	Candida pseudotropicalis	GGTGTACGGATTTGATTAGTTATGT
	Kluyveromyces lactis	GGTGTACGGATTTGATTAGGTATGT

Systemic telomere length and aging

As a measure of systemic telomere length, peripheral blood leukocyte telomere length is generally preferred. Systemic telomere length has been proposed as a marker of biological aging. A subject's systemic telomere length is predominantly genetically determined, but has several other known determinants: age (shorter telomeres in older people), paternal age at birth (longer telomeres in subjects with older fathers at their birth) and sex (shorter telomeres in men, probably due to a faster telomere attrition). Evidence suggests that elevated levels of oxidative stress and inflammation further increase the telomere attrition rate.[16]

Vitamin D may have an effect on peripheral blood leukocyte telomere length. *Richards and coworkers* examined whether vitamin D concentrations would slow the rate of shortening of leukocyte telomeres. The authors stated that vitamin D is a potent inhibitor of the proinflammatory response and slows the turnover of leukocytes. Leukocyte telomere length (LTL) predicts the development of aging-related disease, and the length of these telomeres decreases with each cell division and with increased inflammation. Researchers measured serum vitamin D concentrations in 2160 women, aged 18–79 years (mean age: 49.4), from a large population-based cohort of twins. This study divided the group into thirds, based on vitamin D levels, and found that increased age was significantly associated with shorter LTL ($r = -0.40$, $P < 0.0001$). Higher serum vitamin D concentrations were significantly associated with longer LTL ($r = 0.07$, $P = 0.0010$) and this finding persisted even after adjustment for age ($r = 0.09$, $P < 0.0001$) and other variables that independently could affect LTL (age, season of vitamin D measurement, menopausal status, use of hormone replacement therapy, and physical activity). The difference in LTL between the highest and lowest tertiles of vitamin D was highly significant ($P = 0.0009$) and the authors stated that this was equivalent to 5.0 years of aging. The authors concluded that higher vitamin D levels, easily modifiable through nutritional supplementation, were associated with longer LTL. This underscores the potentially beneficial effects of vitamin D on aging and age-related diseases.[17] Also, peer reviewed clinical studies indicate a relationship between regular exercise and the minimizing of telomere erosion in both mice and humans.[18]

Telomeres and cancer

As a cell begins to become cancerous, it divides more often and its telomeres become very short. If its telomeres get too short, the cell may die. It can escape this fate by becoming a cancer cell and activating an enzyme called telomerase, which prevents the telomeres from getting even shorter.

Studies have found shortened telomeres in many cancers, including pancreatic, bone, prostate, bladder, lung, kidney, and head and neck.

Measuring telomerase may be a new way to detect cancer. If scientists can learn how to stop telomerase, they might be able to fight cancer by making cancer cells age and die. In one experiment, researchers blocked telomerase activity in human breast and prostate cancer cells growing in the laboratory, prompting the tumor cells to die. But

there are risks. Blocking telomerase could impair fertility, wound healing and production of blood cells and immune system cells.

Cancer cells require a mechanism to maintain their telomeric DNA in order to continue dividing indefinitely (immortalization). A mechanism for telomere elongation or maintenance is one of the key steps in cellular immortalization and can be used as a diagnostic marker in the clinic. Telomerase, the enzyme complex responsible for elongating telomeres, is activated in approximately 90% of tumors. However, a sizeable fraction of cancerous cells employ alternative lengthening of telomeres (ALT),[19] a non-conservative telomere lengthening pathway involving the transfer of telomere tandem repeats between sister-chromatids. The mechanism by which ALT is activated is not fully understood because these exchange events are difficult to assess *in vivo*.[20]

Telomerase is the natural enzyme which promotes telomere repair. It is however not active in most cells. It is active in stem cells, germ cells, hair follicles and in 90 percent of cancer cells. Telomerase functions by adding bases to the ends of the telomeres. As a result of this telomerase activity, these cells seem to possess a kind of immortality.

Studies using knockout mice have demonstrated that the role of telomeres in cancer can both be limiting to tumor growth, as well as promote tumorigenesis, depending on the cell type and genomic context.[21] [22]

Telomeres and cardiovascular aging

Shorter (systemic) telomere length has been suggested as an independent risk factor for cardiovascular disease. The origin of this association is unclear and several models have been proposed, particularly attributing the biomarker value to a genetic predisposition in subjects with shorter telomeres, to an effect of inflammation and oxidative stress or to a combination of both.[16]

Telomeres in forensic science

A 2002 Japanese study found that an individual's age can be roughly estimated from the length of their telomeres, making it possible to determine the age of any forensic sample that contains well-preserved DNA.[23] Formerly, forensic scientists were forced to rely on morphological characteristics (such as the growth and decay of bones) to determine an individual's age.[24]

Telomeres in pop culture

The suggested relationship between telomeres and human aging has often been used as an essential plot point in popular fiction, usually well beyond any current scientific understanding.

- Telomeres, and their function in the chromosome reproduction, are referred to as an integral part of the plot of "The Kindred (part 2)" episode of the science fiction television series *Stargate Atlantis*, which first aired in the United States on February 29, 2008, on the Sci-Fi Channel. The image used in the episode is the same as the example at the beginning of this article, which lies in the public domain. The original image was cropped to show a small section from the upper-left corner, and given an orange glow to stand out.
- In the anime series *Gundam SEED* (as well as its sequel, *Mobile Suit Gundam SEED Destiny*), shorter telomeres are given as the reason why clones such as Rey Za Burrel age and die faster than people who were born naturally.
- The novel *Rollback* by Robert J. Sawyer is centered around the idea of lengthening telomeres as a means of increasing one's lifespan.
- In the novel *Turnabout* by Margaret Peterson Haddix, injections stop the telomeres from shortening, supposedly causing the main characters to "unage".
- In the PlayStation 3 game *Metal Gear Solid 4*, Solid Snake was cloned with shortened telomeres, which is the explanation given for his rapid aging.

- In the TV series *Eleventh Hour*, one of the main antagonists, a geneticist with the alias Geppetto, supposedly finds a way to lengthen telomeres thereby reducing the effects of aging on the quality of the host's DNA.
- In the *Area 51* novels by Robert Doherty, the Grail (a fictional alien artifact claimed as the source of the Holy Grail legend) makes humans immortal by giving them the ability to produce telomerase.
- Albedo Piazolla, one of the main villains of the *Xenosaga* series, is a genetically engineered superhuman possessing supernatural regenerative powers that are attributed to him having "infinite telomerase".

See also

- Senescence (Biological aging).
- Rejuvenation (aging)
- Immortality

Further reading

- Weinstein BS, Ciszek D (May 2002), "The reserve-capacity hypothesis: evolutionary origins and modern implications of the trade-off between tumor-suppression and tissue-repair", *Exp. Gerontol.* **37** (5): 615–27, doi:10.1016/S0531-5565(02)00012-8 [25], PMID 11909679 [26] — A paper detailing the evolutionary origins and medical implications of the vertebrate telomere system, including the pervasive trade-off between cancer prevention and damage repair. Also addresses the probable danger posed by the elongation of telomeres in lab mice.
- Cong YS, Wright WE, Shay JW (September 2002), "Human telomerase and its regulation" [27], *Microbiol. Mol. Biol. Rev.* **66** (3): 407–25, table of contents, doi:10.1128/MMBR.66.3.407-425.2002 [28], PMID 12208997 [29], PMC 120798 [30]
- Bassham S, Beam A, Shampay J (January 1998), "Telomere variation in Xenopus laevis" [31], *Mol. Cell. Biol.* **18** (1): 269–75, PMID 9418874 [32], PMC 121490 [33]
- Witzany, G (2008), "). The Viral Origins of Telomeres and Telomerases and their Important Role in Eukaryogenesis and Genome Maintenance." [34], *Biosemiotics"*, doi:10.1007/s12304-008-9018-0 [35]

External links

- Telomeres and Telomerase - A summary [36]
- Telomeres and Telomerase: Their Implications in Human Health and Disease [37] on-line lecture by Elizabeth Blackburn
- Telomeres and Telomerase: The Means to the End [38] Nobel Lecture by Elizabeth Blackburn, which includes a reference to the impact of stress and pessimism on telomeres length
- Telomerase and the Consequences of Telomere Dysfunction [39] Nobel Lecture by Carol Greider
- DNA Ends: Just the Beginning [40] Nobel Lecture by Jack Szostak

References

[1] Olovnikov, Alexei M. (1971). "Принцип маргинотомии в матричном синтезе полинуклеотидов [Principle of marginotomy in template synthesis of polynucleotides]" (in Russian). *Doklady Akademii Nauk SSSR* **201** (6): 1496–9. PMID 5158754 (http://www.ncbi.nlm.nih.gov/pubmed/5158754).

[2] Olovnikov AM (September 1973). "A theory of marginotomy. The incomplete copying of template margin in enzymic synthesis of polynucleotides and biological significance of the phenomenon". *J. Theor. Biol.* **41** (1): 181–90. doi: 10.1016/0022-5193(73)90198-7 (http://dx.doi.org/10.1016/0022-5193(73)90198-7). PMID 4754905 (http://www.ncbi.nlm.nih.gov/pubmed/4754905).

[3] AtGoogleTalks, August 20, 2008 Molecular biologist Elizabeth Blackburn (http://www.youtube.com/watch?v=irUQEG4BSK4)

[4] Harrison's Principles of Internal Medicine, Ch. 69, Cancer cell biology and angiogenesis, Robert G. Fenton and Dan L. Longo, p. 454.

[5] http://nobelprize.org/nobel_prizes/medicine/laureates/2009/press.html

[6] Maloy, Stanley (July 12, 2002). "Bacterial Chromosome Structure" (http://www.sci.sdsu.edu/~smaloy/MicrobialGenetics/topics/chroms-genes-prots/chromosomes.html). . Retrieved 2008-06-22.

[7] http://ndbserver.rutgers.edu/atlas/xray/structures/U/ud0017/ud0017.html

[8] Joeng KS, Song EJ, Lee KJ, Lee J (2004). "Long lifespan in worms with long telomeric DNA". *Nature Genetics* **36** (6): 607–11. doi: 10.1038/ng1356 (http://dx.doi.org/10.1038/ng1356). PMID 15122256 (http://www.ncbi.nlm.nih.gov/pubmed/15122256).

[9] Nakagawa S, Gemmell NJ, Burke T (September 2004). "Measuring vertebrate telomeres: applications and limitations". *Mol. Ecol.* **13** (9): 2523–33. doi: 10.1111/j.1365-294X.2004.02291.x (http://dx.doi.org/10.1111/j.1365-294X.2004.02291.x). PMID 15315667 (http://www.ncbi.nlm.nih.gov/pubmed/15315667).

[10] Juola, Frans A; Haussmann, Mark F; Dearborn, Donald C; Vleck, Carol M (2006). "Telomere shortening in a long-lived marine bird: Cross-sectional analysis and test of an aging tool". *The Auk* **123**: 775. doi: 10.1642/0004-8038(2006)123[775:TSIALM]2.0.CO;2 (http://dx.doi.org/10.1642/0004-8038(2006)123[775:TSIALM]2.0.CO;2).

[11] Tanglao, Shawna, et al. (2008). *The Discovery of C0057684, a Telomerase Activity Inducing Compound* (http://www.mfoundation.org/UABBA/presenting/abstracts/tanglao/). The Methuselah Foundation. .

[12] Effros, et al. (2008). *Geron Scientists and Collaborators Demonstrate TAT2 - A Small Molecule Telomerase Activator - Enhances Antiviral Function of Immune Cells From HIV+ Donors* (http://www.reuters.com/article/pressRelease/idUS126834+10-Nov-2008+BW20081110). Reuters. .

[13] Increased telomerase activity and comprehensive lifestyle changes: a pilot study (http://www.thelancet.com/journals/lanonc/article/PIIS1470204508702341/abstract?isEOP=true)

[14] Lifestyle Changes May Affect How Quickly Cells Age (http://www.findingdulcinea.com/news/health/September-October-08/Lifestyle-Changes-May-Affect-How-Quickly-Cells-Age.html)

[15] Baerlocher GM, Vulto I, de Jong G, Lansdorp PM (2006). "Flow cytometry and FISH to measure the average length of telomeres (flow FISH)". *Nat Protoc* **1** (5): 2365–76. doi: 10.1038/nprot.2006.263 (http://dx.doi.org/10.1038/nprot.2006.263). PMID 17406480 (http://www.ncbi.nlm.nih.gov/pubmed/17406480).

[16] De Meyer T, Rietzschel ER, De Buyzere ML, Van Criekinge W, Bekaert S (2008). "Studying telomeres in a longitudinal population based study". *Front. Biosci.* **13**: 2960–70. doi: 10.2741/2901 (http://dx.doi.org/10.2741/2901). PMID 17981769 (http://www.ncbi.nlm.nih.gov/pubmed/17981769).

[17] Richards JB, Valdes AM, Gardner JP, *et al* (November 2007). "Higher serum vitamin D concentrations are associated with longer leukocyte telomere length in women" (http://www.ajcn.org/cgi/pmidlookup?view=long&pmid=17991655). *Am. J. Clin. Nutr.* **86** (5): 1420–5. PMID 17991655 (http://www.ncbi.nlm.nih.gov/pubmed/17991655). PMC 2196219 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2196219). .

[18] http://circ.ahajournals.org/cgi/content/full/circulationaha;120/24/2405

[19] Henson JD, Neumann AA, Yeager TR, Reddel RR (2002). "Alternative lengthening of telomeres in mammalian cells" (http://www.nature.com/onc/journal/v21/n4/full/1205058a.html). *Oncogene* **21** (4): 598–610. PMID 11850785. .

[20] Chris Molenaar, Karien Wiesmeijer, Nico P. Verwoerd, Shadi Khazen, Roland Eils, Hans J. Tanke, and Roeland W. Dirks (2003-12-15). "Visualizing telomere dynamics in living mammalian cells using PNA probes" (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC291828/). *The EMBO Journal* (The European Molecular Biology Organization) **22** (24): 6631–6641. doi: 10.1093/emboj/cdg633 (http://dx.doi.org/10.1093/emboj/cdg633). PMC 291828 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=291828). . Retrieved 2009-11-25.

[21] Chin L, Artandi SE, Shen Q, *et al.* (May 1999). "p53 deficiency rescues the adverse effects of telomere loss and cooperates with telomere dysfunction to accelerate carcinogenesis". *Cell* **97** (4): 527–38. doi: 10.1016/S0092-8674(00)80762-X (http://dx.doi.org/10.1016/S0092-8674(00)80762-X). PMID 10338216 (http://www.ncbi.nlm.nih.gov/pubmed/10338216).

[22] Greenberg RA, Chin L, Femino A, *et al.* (May 1999). "Short dysfunctional telomeres impair tumorigenesis in the INK4a(delta2/3) cancer-prone mouse". *Cell* **97** (4): 515–25. doi: 10.1016/S0092-8674(00)80761-8 (http://dx.doi.org/10.1016/S0092-8674(00)80761-8). PMID 10338215 (http://www.ncbi.nlm.nih.gov/pubmed/10338215).

[23] Tsuji A, Ishiko A, Takasaki T, Ikeda N (May 2002). "Estimating age of humans based on telomere shortening". *Forensic Sci. Int.* **126** (3): 197–9. doi: 10.1016/S0379-0738(02)00086-5 (http://dx.doi.org/10.1016/S0379-0738(02)00086-5). PMID 12062940 (http://www.ncbi.nlm.nih.gov/pubmed/12062940).

[24] Forensic Science | Forensic Anthropology (http://library.thinkquest.org/04oct/00206/pti_forensic_anthropolgy.htm)

[25] http://dx.doi.org/10.1016%2FS0531-5565%2802%2900012-8

[26] http://www.ncbi.nlm.nih.gov/pubmed/11909679

[27] http://mmbr.asm.org/cgi/pmidlookup?view=long&pmid=12208997

[28] http://dx.doi.org/10.1128%2FMMBR.66.3.407-425.2002

[29] http://www.ncbi.nlm.nih.gov/pubmed/12208997

[30] http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=120798

[31] http://mcb.asm.org/cgi/pmidlookup?view=long&pmid=9418874

[32] http://www.ncbi.nlm.nih.gov/pubmed/9418874

[33] http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=121490

[34] http://www.springerlink.com/content/3907874721566v13

[35] http://dx.doi.org/10.1007%2Fs12304-008-9018-0

[36] http://whyweage.com/node/11

[37] http://ascb.org/ibioseminars/Blackburn/Blackburn1.cfm

[38] http://nobelprize.org/mediaplayer/index.php?id=1214

[39] http://nobelprize.org/mediaplayer/index.php?id=1216

[40] http://nobelprize.org/mediaplayer/index.php?id=1218

DNA polymerase

A **DNA polymerase** is an enzyme that catalyzes the polymerization of deoxyribonucleotides into a DNA strand. DNA polymerases are best-known for their role in DNA replication, in which the polymerase "reads" an intact DNA strand as a template and uses it to synthesize the new strand. This process copies a piece of DNA. The newly-polymerized molecule is complementary to the template strand and identical to the template's original partner strand. DNA polymerases use a magnesium ion for catalytic activity.

3D structure of the DNA-binding helix-turn-helix motifs in human DNA polymerase beta
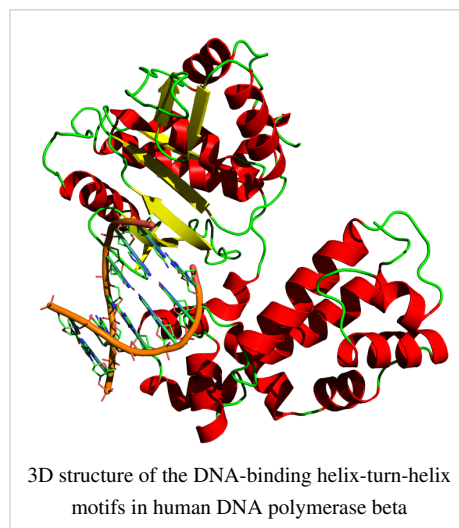
Function

DNA polymerase can add free nucleotides to only the 3' end of the newly-forming strand. This results in elongation of the new strand in a 5'-3' direction. No known DNA polymerase is able to begin a new chain (*de novo*). DNA polymerase can add a nucleotide onto only a preexisting 3'-OH group, and, therefore, needs a primer at which it can add the first nucleotide. Primers consist of RNA and DNA bases with the first two bases always being RNA, and are synthesized by another enzyme called primase. An enzyme known as a helicase is required to unwind DNA from a double-strand structure to a single-strand structure to facilitate replication of each strand consistent with the semiconservative model of DNA replication.

Error correction is a property of some, but not all, DNA polymerases. This process corrects mistakes in newly-synthesized DNA. When an incorrect base pair is recognized, DNA polymerase reverses its direction by one base pair of DNA. The 3'-5' exonuclease activity of the enzyme allows the incorrect base pair to be excised (this activity is known as *proofreading*). Following base excision, the polymerase can re-insert the correct base and replication can continue.

Various DNA polymerases are extensively used in molecular biology experiments.

DNA polymerase with proofreading ability

Variation across species

DNA polymerases have highly-conserved structure, which means that their overall catalytic subunits vary, on a whole, very little from species to species. Conserved structures usually indicate important, irreplicable functions of the cell, the maintenance of which provides evolutionary advantages.

Some viruses also encode special DNA polymerases, such as Hepatitis B virus DNA polymerase. These may selectively replicate viral DNA through a variety of mechanisms. Retroviruses encode an unusual DNA polymerase called reverse transcriptase, which is an RNA-dependent DNA polymerase (RdDp). It polymerizes DNA from a template of RNA.

DNA polymerase families

Based on sequence homology, DNA polymerases can be further subdivided into seven different families: A, B, C, D, X, Y, and RT.

Family A

Polymerases contain both replicative and repair polymerases. Replicative members from this family include the extensively-studied T7 DNA polymerase, as well as the eukaryotic mitochondrial DNA Polymerase γ. Among the repair polymerases are *E. coli* DNA pol I, *Thermus aquaticus* pol I, and *Bacillus stearothermophilus* pol I. These repair polymerases are involved in excision repair and processing of Okazaki fragments generated during lagging strand synthesis.
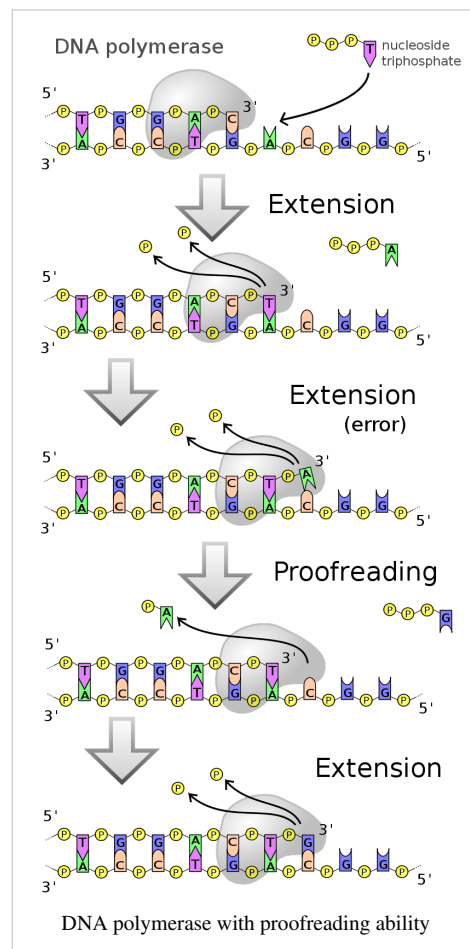
Family B

Polymerases mostly contain replicative polymerases and include the major eukaryotic DNA polymerases α, δ, ε, (see Greek letters) and also DNA polymerase ζ. Family B also includes DNA polymerases encoded by some bacteria and bacteriophages, of which the best-characterized are from T4, Phi29, and RB69 bacteriophages. These enzymes are involved in both leading and lagging strand synthesis during replication. A hallmark of the B family of polymerases is their highly faithful DNA synthesis during replication. While many have an intrinsic 3'-5' proofreading exonuclease activity, eukaryotic DNA polymerases α and ζ are two examples of B family polymerases lacking this proofreading activity.

Family C

Polymerases are the primary bacterial chromosomal replicative enzymes. DNA Polymerase III alpha subunit from *E. coli* is the catalytic subunit [1] and possesses no known nuclease activity. A separate subunit, the epsilon subunit, possesses the 3'-5' exonuclease activity used for editing during chromosomal replication. Recent research has classified Family C polymerases as a subcategory of Family X.

Family D

Polymerases are still not very well characterized. All known examples are found in the Euryarchaeota subdomain of Archaea and are thought to be replicative polymerases.

Family X

Contains the well-known eukaryotic polymerase pol β, as well as other eukaryotic polymerases such as pol σ, pol λ, pol μ, and terminal deoxynucleotidyl transferase (TdT). Pol β is required for short-patch base excision repair, a DNA repair pathway that is essential for repairing abasic sites. Pol λ and Pol μ are involved in non-homologous end-joining, a mechanism for rejoining DNA double-strand breaks. TdT is expressed only in lymphoid tissue, and adds "n nucleotides" to double-strand breaks formed during V(D)J recombination to promote immunological diversity. The yeast *Saccharomyces cerevisiae* has only one Pol X polymerase, Pol4, which is involved in non-homologous end-joining.

Family Y

Polymerases differ from others in having a low fidelity on undamaged templates and in their ability to replicate through damaged DNA. Members of this family are hence called translesion synthesis (TLS) polymerases. Depending on the lesion, TLS polymerases can bypass the damage in an error-free or error-prone fashion, the latter resulting in elevated mutagenesis. Xeroderma pigmentosum variant (XPV) patients for instance have mutations in the gene encoding Pol η (eta), which is error-free for UV-lesions. In XPV patients, alternative error-prone polymerases, e.g., Polζ (zeta) (polymerase ζ is a B Family polymerase a complex of the catalytic subunit REV3L with Rev7, which associates with Rev1[2]), are thought to be involved in mistakes that result in the cancer predisposition of these patients. Other members in humans are Pol ι (iota), Pol κ (kappa), and Rev1 (terminal deoxycytidyl transferase). In E.coli, two TLS polymerases, Pol IV (DINB) and PolV (UmuD'$_2$C), are known.

Family RT

The reverse transcriptase family contains examples from both retroviruses and eukaryotic polymerases. The eukaryotic polymerases are usually restricted to telomerases. These polymerases use an RNA template to synthesize the DNA strand.

Prokaryotic DNA polymerases

Bacteria have 5 known DNA polymerases:

- **Pol I**: implicated in DNA repair; has 5'->3' (Polymerase) activity and both 3'->5' exonuclease (Proofreading) and 5'->3' exonuclease activity (RNA Primer removal).
- **Pol II**: involved in reparation of damaged DNA; has 3'->5' exonuclease activity.
- **Pol III**: the main polymerase in bacteria (elongates in DNA replication); has 3'->5' exonuclease proofreading ability.
- **Pol IV**: a Y-family DNA polymerase.
- **Pol V**: a Y-family DNA polymerase; participates in bypassing DNA damage.

Eukaryotic DNA polymerases

Eukaryotes have at least 15 DNA Polymerases:[3]

- **Pol α** (synonyms are RNA primase, **DNA** polymerase): forms a complex with a small catalytic (PriS) and a large noncatalytic (PriL) subunit[4] , with the Pri subunits acting as a primase (synthesizing an RNA primer), and then with DNA Pol α elongating that primer with DNA nucleotides. After around 20 nucleotides[5] elongation is taken over by Pol ε (on the leading strand) and δ (on the lagging strand).
- **Pol β**: Implicated in repairing DNA, in base excision repair and gap-filling synthesis.
- **Pol γ**: Replicates and repairs mitochondrial DNA and has proofreading 3'->5' exonuclease activity.
- **Pol δ**: Highly processive and has proofreading 3'->5' exonuclease activity. Thought to be the main polymerase involved in lagging strand synthesis, though there is still debate about its role[6] .
- **Pol ε**: Also highly processive and has proofreading 3'->5' exonuclease activity. Highly related to pol δ, and thought to be the main polymerase involved in leading strand synthesis[7] , though there is again still debate about its role[6] .
- **η**, **ι**, **κ**, and **Rev1** are Y-family DNA polymerases and **Pol ζ** is a B-family DNA polymerase. These polymerases are involved in the bypass of DNA damage.[8]
- There are also other eukaryotic polymerases known, which are not as well characterized: **θ**, **λ**, **φ**, **σ**, and **μ**.

None of the eukaryotic polymerases can remove primers (5'->3' exonuclease activity); that function is carried out by other enzymes. Only the polymerases that deal with the elongation (γ, δ and ε) have proofreading ability (3'->5' exonuclease).

See also

- Polymerase chain reaction
- RNA polymerase
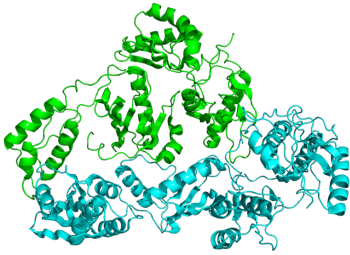
External links

- Burgers P, Koonin E, Bruford E et al. (2001). "Eukaryotic DNA polymerases: proposal for a revised nomenclature". *J. Biol. Chem.* **276** (47): 43487–90. doi:10.1074/jbc.R100056200 [9]. PMID 11579108 [10].
- PDB Molecule of the Month *pdb3_1* [11]
- Unusual repair mechanism in DNA polymerase lambda [12], Ohio State University, July 25, 2006.
- MeSH *DNA+polymerases* [13]
- EC 2.7.7.7 [14]
- A great animation of DNA Polymerase from WEHI [15]

References

[1] Lamers, M.; Georgescu, R.; Lee, S.; O'Donnell, M.; Kuriyan, J. (2006). "Crystal structure of the catalytic alpha subunit of E. Coli replicative DNA polymerase III". *Cell* **126** (5): 881–892. doi: 10.1016/j.cell.2006.07.028 (http://dx.doi.org/10.1016/j.cell.2006.07.028). PMID 16959568 (http://www.ncbi.nlm.nih.gov/pubmed/16959568).

[2] Gan GN; Wittschieben JP; Wittschieben BØ; Wood RD (2008). "DNA polymerase zeta (pol zeta) in higher eukaryotes". *Cell Research* **18**: 174–83. PMID 18157155 (http://www.ncbi.nlm.nih.gov/pubmed/18157155).

[3] I. Hubscher, U.; Maga, G.; Spadari, S. (2002). "Eukaryotic DNA polymerases". *Annual Review of Biochemistry* **71**: 133. doi: 10.1146/annurev.biochem.71.090501.150041 (http://dx.doi.org/10.1146/annurev.biochem.71.090501.150041). PMID 12045093 (http://www.ncbi.nlm.nih.gov/pubmed/12045093).

[4] Elizabeth R. Barry; Stephen D. Bell (12/2006). "DNA Replication in the Archaea". *Microbiology and Molecular Biology Reviews* **70**: 876–887. doi: 10.1128/MMBR.00029-06 (http://dx.doi.org/10.1128/MMBR.00029-06). PMID 17158702 (http://www.ncbi.nlm.nih.gov/pubmed/17158702).

[5] J. M. Berg; J. L. Tymoczko; L. Stryer "Biochemie", Springer, Heidelberg/Berlin 2003

[6] Scott D McCulloch; Thomas A Kunkel (01/2008). "The fidelity of DNA synthesis by eukaryotic replicative and translesion synthesis polymerases". *Cell Research* **18**: 148. doi: 10.1038/cr.2008.4 (http://dx.doi.org/10.1038/cr.2008.4). PMID 18166979 (http://www.ncbi.nlm.nih.gov/pubmed/18166979).

[7] Pursell, Z.F. et al. (2007). "Yeast DNA Polymerase ε Participates in Leading-Strand DNA Replication". *Science* **317**: 127. doi: 10.1126/science.1144067 (http://dx.doi.org/10.1126/science.1144067). PMID 17615360 (http://www.ncbi.nlm.nih.gov/pubmed/17615360).

[8] I. Prakash, S.; Johnson, R. E.; Prakash, L. (2005). "Eukaryotic translesion synthesis DNA polymerases: specificity of structure and function". *Annual Review of Biochemistry* **74**: 317. doi: 10.1146/annurev.biochem.74.082803.133250 (http://dx.doi.org/10.1146/annurev.biochem.74.082803.133250). PMID 15952890 (http://www.ncbi.nlm.nih.gov/pubmed/15952890).

[9] http://dx.doi.org/10.1074%2Fjbc.R100056200

[10] http://www.ncbi.nlm.nih.gov/pubmed/11579108

[11] http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb3_1.html

[12] http://researchnews.osu.edu/archive/repprot.htm

[13] http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=DNA+polymerases

[14] http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.7.7

[15] http://www.wehi.edu.au/education/wehi-tv/dna/replication.html

Reverse transcriptase

<table>
<tr><td colspan="2" align="center">Reverse transcriptase
(RNA-dependent DNA polymerase)</td></tr>
<tr><td colspan="2" align="center"></td></tr>
<tr><td colspan="2">Crystallographic structure of HIV reverse transcriptase where the P51 subunit is colored green and the P66 subunit is colored cyan.[1]</td></tr>
<tr><td colspan="2" align="center">Identifiers</td></tr>
<tr><td>Symbol</td><td>RVT_1</td></tr>
<tr><td>Pfam</td><td>PF00078 [2]</td></tr>
<tr><td>InterPro</td><td>IPR000477 [3]</td></tr>
<tr><td>PROSITE</td><td>PS50878 [4]</td></tr>
<tr><td>SCOP</td><td>1hmv [5]</td></tr>
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<table>
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<tr><td>BRENDA</td><td>BRENDA entry [149]</td></tr>
<tr><td>ExPASy</td><td>NiceZyme view [150]</td></tr>
<tr><td>KEGG</td><td>KEGG entry [151]</td></tr>
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MetaCyc	metabolic pathway [152]
PRIAM	profile [153]
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In the fields of molecular biology and biochemistry, a **reverse transcriptase**, also known as **RNA-dependent DNA polymerase**, is a DNA polymerase enzyme that transcribes single-stranded RNA into double-stranded DNA. It also helps in the formation of a double helix DNA once the RNA has been reverse transcribed into a single strand cDNA. Normal transcription involves the synthesis of RNA from DNA; hence, reverse transcription is the *reverse* of this.

Reverse transcriptase was discovered by Howard Temin at the University of Wisconsin–Madison, and independently by David Baltimore in 1970 at MIT. The two shared the 1975 Nobel Prize in Physiology or Medicine with Renato Dulbecco for their discovery.

Well studied reverse transcriptases include:

- HIV-1 reverse transcriptase from human immunodeficiency virus type 1 (PDB 1HMV [159])
- M-MLV reverse transcriptase from the Moloney murine leukemia virus
- AMV reverse transcriptase from the avian myeloblastosis virus
- Telomerase reverse transcriptase that maintains the telomeres of eukaryotic chromosomes

Function in viruses

The enzyme is encoded and used by reverse-transcribing viruses, which use the enzyme during the process of replication. Reverse-transcribing RNA viruses, such as retroviruses, use the enzyme to reverse-transcribe their RNA genomes into DNA, which is then integrated into the host genome and replicated along with it. Reverse-transcribing DNA viruses, such as the hepadnaviruses, can allow RNA to serve as a template in assembling, and making DNA strands. HIV infects humans with the use of this enzyme. Without reverse transcriptase, the viral genome would not be able to incorporate into the host cell, resulting in the failure of the ability to replicate. Unlike bacteria, retroviruses use preexisting host-encoded transfer RNAs as primers.

Process of reverse transcription

Reverse transcriptase creates single stranded DNA from an RNA template.

In virus species with reverse transcriptase lacking DNA-dependent DNA polymerase activity, creation of double-stranded DNA can possibly be done by host-encoded DNA polymerase δ, mistaking the viral DNA-RNA for a primer and synthesizing a double-stranded DNA by similar mechanism as in primer removal, where the newly synthesized DNA displaces the original RNA template.

The process of reverse transcription is extremely error-prone and it is during this step that mutations may occur. Such mutations may cause drug resistance.

Process in class VI viruses

Class VI viruses ssRNA-RT, also called the retroviruses are RNA reverse transcribing viruses with a DNA intermediate. Their genomes consist of two molecules of positive sense single stranded RNA with a 5' cap and 3' polyadenylated tail. Examples of retroviruses include *Human Immunodeficiency Virus* (HIV) and *Human T-Lymphotropic virus* (HTLV). Creation of double-stranded DNA occurs in the cytosol[160] as a series of steps:

1. A specific cellular tRNA acts as a primer and hybridizes to a complementary part of the virus genome called the primer binding site or PBS

2. Complementary DNA then binds to the U5 (non-coding region) and R region (a direct repeat found at both ends of the RNA molecule) of the viral RNA

3. A domain on the reverse transcriptase enzyme called RNAse H degrades the 5' end of the RNA which removes the U5 and R region

4. The primer then 'jumps' to the 3' end of the viral genome and the newly synthesised DNA strands hybridizes to the complementary R region on the RNA

5. The first strand of complementary DNA (cDNA) is extended and the majority of viral RNA is degraded by RNAse H

6. Once the strand is completed, second strand synthesis is initiated from the viral RNA

7. There is then another 'jump' where the PBS from the second strand hybridizes with the complementary PBS on the first strand

8. Both strands are extended further and can be incorporated into the hosts genome by the enzyme integrase
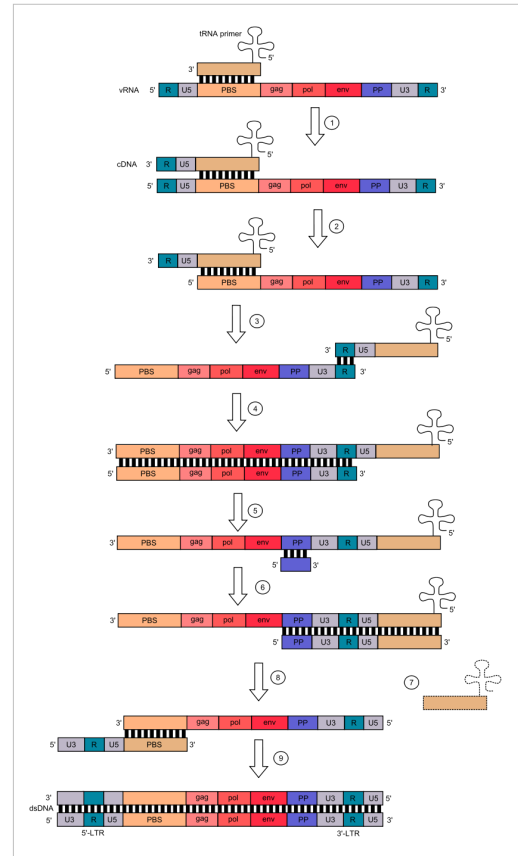
Creation of double-stranded DNA also involves *strand transfer*, in which there is a translocation of short DNA product from initial RNA dependent DNA synthesis to acceptor template regions at the other end of the genome, which are later reached and processed by the reverse transcriptase for its DNA-dependent DNA activity.[161]

Retroviral RNA is arranged in 5' terminus to 3' terminus. The site where the primer is annealed to viral RNA is called the primer-binding site (PBS). The RNA 5'end to the PBS site is called U5, and the RNA 3' end to the PBS is called the leader. The tRNA primer is unwound between 14 and 22 nucleotides and forms a base-paired duplex with the viral RNA at PBS. That PBS locates near the 5' terminus of viral RNA is unusual because reverse transcriptase synthesize DNA from 3' end of the primer in the 5' to 3' direction. Therefore, the primer and reverse transcriptase must be relocated to 3' end of viral RNA. In order to accomplish this reposition, multiple steps and various enzymes including DNA polymerase, ribonuclease H(RNase H) and polynucleotide unwinding are needed.[162]

The HIV reverse transcriptase also has ribonuclease activity that degrades the viral RNA during the synthesis of cDNA, as well as DNA-dependent DNA polymerase activity that copies the sense cDNA strand into an *antisense* DNA to form a double-stranded viral DNA intermediate (vDNA).[163]

In eukaryotes

Self-replicating stretches of eukaryotic genomes known as retrotransposons utilize reverse transcriptase to move from one position in the genome to another via a RNA intermediate. They are found abundantly in the genomes of plants and animals. Telomerase is another reverse transcriptase found in many eukaryotes, including humans, which carries its own RNA template; this RNA is used as a template for DNA replication.[164] [165]

In prokaryotes

Reverse transcriptases are also found in bacterial Retron msr RNAs, distinct sequences which code for reverse transcriptase, and are used in the synthesis of msDNA. In order to initiate synthesis of DNA, a primer is needed. In bacteria, the primer is synthesized during replication.[166]

Structure

Reverse transcriptase enzymes include an RNA-dependent DNA polymerase and a DNA-dependent DNA polymerase, which work together to perform transcription. In addition to the transcription function, retroviral reverse transcriptases have a domain belonging to the RNase H family which is vital to their replication.

Replication fidelity

There are three different replication systems during the life cycle of a retrovirus. First of all, the reverse transcriptase synthesize viral DNA from viral RNA, and then from newly made complementary DNA strand. The second replication process occurs when host cellular DNA polymerase replicates the integrated viral DNA. Lastly, RNA polymerase II transcribes the proviral DNA into RNA which will be packed into virions. Therefore, mutation can occur during one or all of these replication steps.[167]

Reverse transcriptase has a high error rate when transcribing RNA into DNA since, unlike DNA polymerases, it has no proofreading ability. This high error rate allows mutations to accumulate at an accelerated rate relative to proofread forms of replication. The commercially available reverse transcriptases produced by Promega are quoted by their manuals as having error rates in the range of 1 in 17,000 bases for AMV and 1 in 30,000 bases for M-MLV[168]

Applications

Antiviral drugs

As HIV uses reverse transcriptase to copy its genetic material and generate new viruses (part of a retrovirus proliferation circle), specific drugs have been designed to disrupt the process and thereby suppress its growth. Collectively, these drugs are known as reverse transcriptase inhibitors and include the nucleoside and nucleotide analogues zidovudine (trade name Retrovir), lamivudine (Epivir) and tenofovir (Viread), as well as non-nucleoside inhibitors, such as nevirapine (Viramune).

The molecular structure of zidovudine (AZT), a drug used to inhibit HIV reverse transcriptase

Molecular biology

Reverse transcriptase is commonly used in research to apply the polymerase chain reaction technique to RNA in a technique called reverse transcription polymerase chain reaction (RT-PCR). The classical PCR technique can be applied only to DNA strands, but, with the help of reverse transcriptase, RNA can be transcribed into DNA, thus making PCR analysis of RNA molecules possible. Reverse transcriptase is used also to create cDNA libraries from mRNA. The commercial availability of reverse transcriptase greatly improved knowledge in the area of molecular biology, as, along with other enzymes, it allowed scientists to clone, sequence, and characterise DNA.
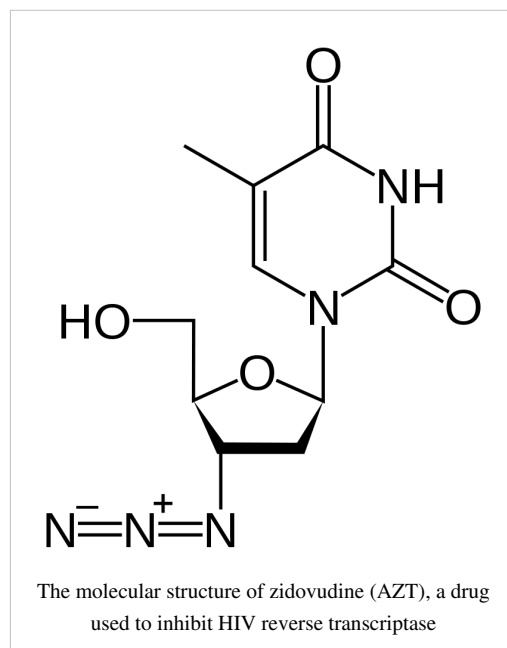
History

The idea of reverse transcription was very unpopular at first as it contradicted the central dogma of molecular biology which states that DNA is transcribed into RNA which is then translated into proteins. However, in 1970 when the scientists Howard Temin and David Baltimore both independently discovered the enzyme responsible for reverse transcription, named reverse transcriptase, the possibility that genetic information could be passed on in this manner was finally accepted.

See also

- cDNA library
- DNA polymerase
- msDNA
- Reverse transcribing virus
- RNA polymerase
- Telomerase
- Retrotransposon marker

External links

- MeSH *RNA+Transcriptase* [169]
- animation of reverse transcriptase action and three reverse transcriptase inhibitors [170]
- Molecule of the month [171] (September 2002) at the Protein Data Bank
- HIV Replication 3D Medical Animation. (Nov 2008). Video by Boehringer Ingelheim. [172]

References

[1] PDB 1HMV (http://www.rcsb.org/pdb/explore/explore.do?structureId=1HMV); Rodgers DW, Gamblin SJ, Harris BA, Ray S, Culp JS, Hellmig B, Woolf DJ, Debouck C, Harrison SC (February 1995). "The structure of unliganded reverse transcriptase from the human immunodeficiency virus type 1" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=42671). *Proc. Natl. Acad. Sci. U.S.A.* **92** (4): 1222–6. PMID 7532306 (http://www.ncbi.nlm.nih.gov/pubmed/7532306).

[2] http://pfam.sanger.ac.uk/family?acc=PF00078

[3] http://www.ebi.ac.uk/interpro/DisplayIproEntry?ac=IPR000477

[4] http://www.expasy.org/cgi-bin/prosite-search-ac?PS50878

[5] http://scop.mrc-lmb.cam.ac.uk/scop/search.cgi?tlev=fa;&pdb=1hmv

[6] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1bqm

[7] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1bqn

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[92] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1tv6
[93] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1tvr
[94] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1uwb
[95] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1vrt
[96] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1vru
[97] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1ztt
[98] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1ztw
[99] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2b5j
[100] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2b6a
[101] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2ban
[102] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2be2
[103] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2fjv
[104] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2fjw
[105] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2fjx

[106] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2fvp
[107] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2fvq
[108] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2fvr
[109] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2fvs
[110] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2hmi
[111] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2hnd
[112] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2hny
[113] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2hnz
[114] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2i5j
[115] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2iaj
[116] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2ic3
[117] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2opp
[118] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2opq
[119] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2opr
[120] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2ops
[121] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2r2r
[122] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2r2s
[123] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2r2t
[124] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2r2u
[125] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2rf2
[126] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2rki
[127] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2vg5
[128] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2vg6
[129] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2vg7
[130] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2zd1
[131] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2ze2
[132] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3bgr
[133] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3c6t
[134] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3c6u
[135] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3di6
[136] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3dle
[137] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3dlg
[138] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3dlk
[139] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3dm2
[140] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3dok
[141] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3dol
[142] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3drp
[143] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3drr
[144] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3drs
[145] http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3hvt
[146] http://www.chem.qmul.ac.uk/iubmb/enzyme/EC2/7/7/49.html
[147] http://toolserver.org/~magnus/cas.php?language=en&cas=9068-38-6&title=
[148] http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=2.7.7.49
[149] http://www.brenda-enzymes.org/php/result_flat.php4?ecno=2.7.7.49
[150] http://www.expasy.org/enzyme/2.7.7.49
[151] http://www.genome.ad.jp/dbget-bin/www_bget?enzyme+2.7.7.49
[152] http://biocyc.org/META/substring-search?type=NIL&object=2.7.7.49
[153] http://bioinfo.genopole-toulouse.prd.fr/priam/cgi-bin/PRIAM_profiles_CurrentRelease.pl?EC=2.7.7.49
[154] http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/enzymes/GetPage.pl?ec_number=2.7.7.49
[155] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?query=GO:0003964&view=details
[156] http://www.ebi.ac.uk/ego/DisplayGoTerm?id=GO:0003964&format=normal
[157] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&term=2.7.7.49%5BEC/
    RN%20Number%5D%20AND%20pubmed%20pmc%20local%5Bsb%5D
[158] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&term=2.7.7.49%5BEC/RN%20Number%5D
[159] http://www.rcsb.org/pdb/explore/explore.do?structureId=1HMV
[160] Bio-Medicine.org - Retrovirus (http://www.bio-medicine.org/biology-definition/Retrovirus/) Retrieved on 17 Feb, 2009
[161] Telesnitsky, A., Goff, S.P. (1993). "Strong-stop strand transfer during reverse transcription". in Skalka, M. A., Goff, S.P. *Reverse transcriptase* (1st ed.). New York: Cold Spring Harbor. p. 49. ISBN 0-87969-382-7.

[162] Bernstein, A.; Weiss, Robin; Tooze, John (1985). "RNA tumor viruses". *Molecular Biology of Tumor Viruses* (2nd ed.). Cold Spring Harbor, N.Y: Cold Spring Harbor Laboratory.

[163] Doc Kaiser's Microbiology Home Page > IV. VIRUSES > F. ANIMAL VIRUS LIFE CYCLES > 3. The Life Cycle of HIV (http:// student.ccbcmd.edu/courses/bio141/lecguide/unit3/viruses/hivlc.html) Community College of Baltimore County. Updated: Jan., 2008

[164] Monty Krieger; Matthew P Scott; Matsudaira, Paul T.; Lodish, Harvey F.; Darnell, James E.; Lawrence Zipursky; Kaiser, Chris; Arnold Berk (2004). *Molecular cell biology* (5th ed.). New York: W.H. Freeman and CO. ISBN 0-7167-4366-3.

[165] Witzany G (August 2008). "The Viral Origins of Telomeres and Telomerases and their Important Role in Eukaryogenesis and Genome Maintenance". *Biosemiotics* **1** (2): 191–206. doi: 10.1007/s12304-008-9018-0 (http://dx.doi.org/10.1007/s12304-008-9018-0).

[166] Hurwitz J, Leis JP (January 1972). "RNA-dependent DNA polymerase activity of RNA tumor viruses. I. Directing influence of DNA in the reaction" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=356270). *J. Virol.* **9** (1): 116–29. PMID 4333538 (http://www.ncbi.nlm.nih.gov/pubmed/4333538).

[167] Bbenek, K., Kunkel, A. T (1993). "The fidelity of retroviral reverse transcriptases". in Skalka, M. A., Goff, P. S.. *Reverse transcriptase*. New York: Cold Spring Harbor Laboratory Press. p. 85. ISBN 0-87969-382-7.

[168] Promega kit instruction manual (1999) (http://www.promega.com/pnotes/71/7807_22/7807_22_core.pdf)

[169] http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=RNA+Transcriptase

[170] http://www.tibotec.com/bgdisplay.jhtml?itemname=HIV_discovery&product=none&s=2

[171] http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb33_1.html

[172] http://www.youtube.com/watch?v=RO8MP3wMvqg

Telomerase

Telomerase is an enzyme that adds DNA sequence repeats ("TTAGGG" in all vertebrates) to the 3' end of DNA strands in the telomere regions, which are found at the ends of eukaryotic chromosomes. The telomeres contain condensed DNA material, giving stability to the chromosomes. The enzyme is a reverse transcriptase that carries its own RNA molecule, which is used as a template when it elongates telomeres, which are shortened after each replication cycle. The existence of a compensatory shortening of telomere (telomerase) mechanism was first predicted by Soviet biologist Alexey Olovnikov in 1973[1] , who also suggested the Telomere hypothesis of ageing and the Telomere relations to cancer. Telomerase

A conceptual diagram showing the protein component of telomerase (TERT) in grey and the RNA component (TR) in yellow.

was discovered by Carol W. Greider and Elizabeth Blackburn in 1985 in the ciliate *Tetrahymena*.[2] Together with Jack W. Szostak, Greider and Blackburn were awarded the 2009 Nobel Prize in Physiology or Medicine for their discovery.[3] There are some indicators that telomerase is of retroviral origin.[4]
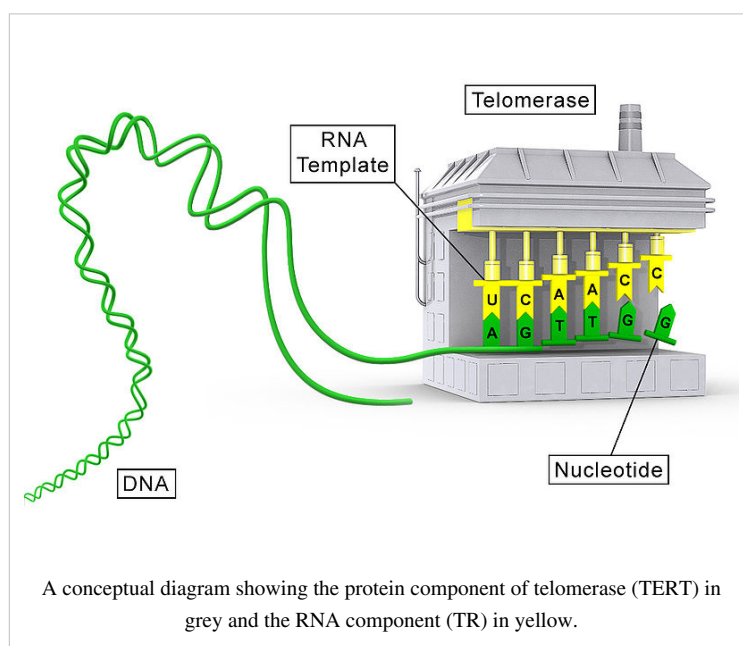
Structure

The protein composition of human telomerase was identified in 2007 by Scott Cohen and his team at the Children's Medical Research Institute in Australia. It consists of two molecules each of human Telomerase Reverse Transcriptase (TERT), Telomerase RNA (TR or TERC), and dyskerin(DKC1).[5] The genes of telomerase subunits, which are TERT,[6] TERC,[7] DKC1,[8] and TEP1[9] *etc*, are located on the different chromosomes in human genome. Human TERT gene(hTERT) is translated into a protein of 1132 amino acids.[10] TERT proteins are sequenced in many eukaryotes[11] . TERT polypeptide folds with TERC, a non-coding RNA (451 nucleotides long in

human). TERT has a 'mitten' structure that allows it to wrap around the chromosome to add single-stranded telomere repeats.

TERT is a reverse transcriptase, which is a class of enzyme that creates single-stranded DNA using single-stranded RNA as a template. Enzymes of this class (not TERT specifically, but the ones isolated from viruses) are utilized by scientists in the molecular biological process of Reverse Transcriptase PCR (RT-PCR), which allows the creation of several DNA copies of a target sequence using RNA as a template. As stated above, TERT carries its own template around, TERC.

The high-resolution protein structure of the *Tribolium castaneum* catalytic subunit of telomerase TERT was decoded in 2008 by Emmanuel Skordalakes and his team at The Wistar Institute in Philadelphia.[12] The structure revealed that the protein consists of four conserved domains (RNA-Binding Domain (TRBD), fingers, palm and thumb), organized into a ring configuration that shares common features with retroviral reverse transcriptases, viral RNA polymerases and bacteriophage B-family DNA polymerases.

Function

By using TERC, TERT can add a six-nucleotide repeating sequence, 5'-TTAGGG (in all vertebrates, the sequence differs in other organisms) to the 3' strand of chromosomes. These TTAGGG repeats (with their various protein binding partners) are called telomeres. The template region of TERC is 3'-CAAUCCCAAUC-5'.[13] This way, telomerase can bind the first few nucleotides of the template to the last telomere sequence on the chromosome, add a new telomere repeat (5'-GGTTAG-3') sequence, let go, realign the new 3'-end of telomere to the template, and repeat the process. (For an explanation on why this elongation is necessary see Telomere shortening.)

Clinical implications

Aging

The enzyme telomerase allows for replacement of short bits of DNA known as telomeres, which are otherwise shortened when a cell divides via mitosis.

In normal circumstances, without the presence of telomerase, if a cell divides recursively, at some point all the progeny will reach their Hayflick limit.[14] With the presence of telomerase, each dividing cell can replace the lost bit of DNA, and any single cell can then divide unbounded. While this unbounded growth property has excited many researchers, caution is warranted in exploiting this property, as exactly this same unbounded growth is a crucial step in enabling cancerous growth.

Embryonic stem cells express telomerase, which allows them to divide repeatedly and form the individual. In adults, telomerase is highly expressed in cells that need to divide regularly (e.g., in the immune system), whereas most somatic cells express it only at very low levels in a cell-cycle-dependent manner.

A variety of premature aging syndromes are associated with short telomeres.[15] These include Werner syndrome, Ataxia telangiectasia, Bloom syndrome, Fanconi anemia, Nijmegen breakage syndrome, and ataxia telangiectasia-like disorder. The genes that have been mutated in these diseases all have roles in the repair of DNA damage, and their precise roles in maintaining telomere length are an active area of investigation. While it is currently unknown to what extent telomere erosion contributes to the normal aging process, maintenance of DNA in general and telomeric DNA, to be specific, have emerged as major players. Dr. Michael Fossel has suggested in an interview [16] that telomerase therapies may be used not only to combat cancer but also to actually get around human aging and extend lifespan significantly. He believes human trials of telomerase-based therapies for extending lifespan will occur within the next 10 years. This timeline is significant because it coincides with the retirement of Baby Boomers in the United States and Europe.

Some experiments have raised questions on whether telomerase can be used as an anti-aging therapy, namely, the fact mice with elevated levels of telomerase have higher cancer incidence and hence do not live longer. In addition, although certain premature aging syndromes have been associated with telomere shortening, mice without active telomerase do not appear to suffer from premature aging. Telomerase also favors tumorogenesis, leading to questions about its potential as an anti-aging therapy.[17] On the other hand, one study showed that activating telomerase in cancer-resistant mice by overexpressing its catalytic subunit extended lifespan.[18] The potential remains for telomerase activators to contribute to the development of cancer.

Since 2007, several compounds have been discovered that cause somatic cells to express higher levels of telomerase than usual. In April 2007, Geron Corporation licensed New York-based company TA Sciences to conduct human trials on a molecule called TA-65, a derivative of Astragalus propinquus, that acts as telomerase activator.[19] In November 2007, Sierra Sciences announced that they had discovered a compound called C0057684 that causes the expression of even higher levels of telomerase activity in somatic cells[20] and, in 2009, announced that they had discovered an additional 62 compounds that cause telomerase activation.[21]

A study in 2009, which focused on Ashkenazi Jews, found that those that live the longest inherit a hyperactive version of telomerase that rebuilds telomeres.[22]

Cancer

When cells are approaching the Hayflick limit in cell cultures, the time to senescence can be extended by the inactivation of the tumor suppressor proteins - TP53 and Retinoblastoma protein (pRb). Cells that have been so-altered will eventually undergo an event termed a "crisis" when the majority of the cells in the culture die. Sometimes, a cell does not stop dividing once it reaches crisis. In a typical situation, the telomeres are lost, and the integrity of the chromosomes declines with every subsequent cell division. Exposed chromosome ends are interpreted as double-stranded breaks (DSB) in DNA; such damage is usually repaired by reattaching (religating) the broken ends together. When the cell does this due to telomere-shortening, the ends of different chromosomes can be attached together. This temporarily solves the problem of lacking telomeres; but, during anaphase of cell division, the fused chromosomes are randomly ripped apart, causing many mutations and chromosomal abnormalities. As this process continues, the cell's genome becomes unstable. Eventually, either sufficient damage will be done to the cell's chromosomes such that cell dies (via programmed cell death, apoptosis), or an additional mutation that activates telomerase will take place.

With the activation of telomerase, some types of cells and their offspring become immortal, that is, their chromosomes will not become unstable no matter how many cell divisions they undergo (they bypass the Hayflick limit), thus avoiding cell death as long as the conditions for their duplication are met. Many cancer cells are considered 'immortal' because telomerase activity allows them to divide virtually forever, which is why they can form tumors. A good example of cancer cells' immortality is HeLa cells, which have been used in laboratories as a model cell line since 1951. They are indeed immortal - daily production of HeLa cells is estimated at several tons even up to this day.

While this method of modeling human cancer in cell culture is effective and has been used for many years by scientists, it is also very imprecise. The exact changes that allow for the formation of the tumorigenic clones in the above-described experiment are not clear. Scientists have subsequently been able to address this question by the serial introduction of several mutations present in a variety of human cancers. This has led to the elucidation of several combinations of mutations that are sufficient for the formation of tumorigenic cells, in a variety of cell types. While the combination varies depending on the cell type, a common theme is that the following alterations are required: activation of TERT, loss of p53 pathway function, loss of pRb pathway function, activation of the Ras or myc proto-oncogenes, and aberration of the PP2A protein phosphatase. That is to say, the cell has an activated telomerase, eliminating the process of death by chromosome instability or loss, absence of apoptosis-induction pathways, and continued activation of mitosis.

This model of cancer in cell culture accurately describes the role of telomerase in actual human tumors. Telomerase activation has been observed in ~90% of all human tumors, suggesting that the immortality conferred by telomerase plays a key role in cancer development. Of the tumors that have not activated TERT,[23] most have found a separate pathway to maintain telomere length termed ALT (Alternative Lengthening of Telomeres).[24] The exact mechanism behind telomere maintenance in the ALT pathway has not been elucidated, but likely involves multiple recombination events at the telomere.

Additional roles in cancer, heart disease, and a socioeconomic and quality of life aspect

Additional roles for telomerase per work by Elizabeth Blackburn *et al.*, include the upregulation of 70 genes known or suspected in cancers' growth and spread through the body, and the activation of glycolysis, which enables cancer cells to rapidly use sugar to facilitate their programmed growth rate.(roughly the growth rate of a fetus)

E. V. Gostjeva *et al.* (MIT) recently imaged colon cancer stem cells and compared them to fetal colon stem cells trying to make a new colon; they were the same.

Elizabeth Blackburn *et al.* UCSF has shown work that reveals that mothers caring for their very sick children have shorter telomeres when they report that their emotional stress is at the greatest point. She also found telomerase active at the site of blockages in coronary artery tissue. This could be why heart attacks can come on so suddenly: Telomerase is driving the growth of the blockage.

Other work has shown that the poor of society have shorter telomeres than the rich.[25] Short telomeres can lead to telomeric crisis and the initiation of cancer if many other conditions are also met, or so the discussion goes at this point.

Blackburn and the two other co-discoverers of telomerase won the Lasker Award (2006), and the Nobel Prize (2009) for the discovery of telomerase and subsequent work on telomerase. Blackburn also won the 2006 Gruber Genetics Prize for same.

Role in other human diseases

Mutations in TERT have been implicated in predisposing patients to aplastic anemia, a disorder in which the bone marrow fails to produce blood cells, in 2005.[26]

Cri du chat Syndrome (CdCS) is a complex disorder involving the loss of the distal portion of the short arm of chromosome 5. TERT is located in the deleted region, and loss of one copy of TERT has been suggested as a cause or contributing factor of this disease.[27]

Dyskeratosis congenita (DC) is a disease of the bone marrow that can be caused by some mutations in the telomerase subunits.[28] In the DC cases, about 35% cases are X-linked-recessive on the DKC1 locus[29] and 5% cases are autosomal dominant on the TERT[30] and TERC[31] loci.

Patients with DC have severe bone marrow failure manifesting as abnormal skin pigmentation, leucoplakia (a white thickening of the oral mucosa), and nail dystrophy, as well as a variety of other symptoms. Individuals with either TERC or DKC1 mutations have shorter telomeres and defective telomerase activity *in vitro* than other individuals of the same age.[32]

There has also been one family in which autosomal dominant DC has been linked to a heterozygous mutation in TERT.[33] These patients also exhibited an increased rate of telomere-shortening, and genetic anticipation (i.e., the DC phenotype worsened with each generation).

Telomerase as a potential drug target

Cancer is a very difficult disease to fight because the immune system has trouble recognizing it, and cancer cells are immortal; they will always continue dividing. Because telomerase is necessary for the immortality of so many cancer types, it is thought to be a potential drug target. If a drug can be used to turn off telomerase in cancer cells, the above process of telomere-shortening will resume—telomere length will be lost as the cells continue to divide, mutations will occur, and cell stability will decrease. Experimental drug and vaccine therapies targeting active telomerase have been tested in mouse models, and some have now entered early clinical trials. Geron Corporation is currently conducting four human clinical trials involving telomerase inhibition and telomerase vaccination. Merck, as a licensee of Geron, has recent approval of an IND for one vaccine type. The vaccine platform is being tested (and now jointly with Merck) using three different approaches. One vaccine is adenovirus/plasmid based (Merck IND). The second is an autologous dendritic cell based vaccine (GRNVAC1), formerly called TVAX when tested in Phase I clinical trials in Prostate Cancer, and it showed significant PSA doubling times as well as T-cell response. Geron's embryonic stem cell derived dendritic cell vaccine targeting telomerase is the third approach and is currently at the pre-clinical stage. These vaccine methods attempt to teach the human immune system to attack cancer cells expressing telomerase. Geron's telomerase inhibitor drug (GRN163L) attempts to stop cancer cell proliferation by inhibiting telomerase and it is in three separate early stage human clinical trials. Indeed, telomerase inhibition in many types of cancer cells grown in culture has led to the massive death of the cell population. However, a variety of caveats, including the presence of the ALT pathway,[23] [24] complicate such therapies. Some have reported ALT methods of telomere maintenance and storage of DNA in cancer stem cells, however Geron claims to have killed cancer stem cells with their telomerase inhibitor GRN163L at Johns Hopkins. GRN163L binds directly to the RNA template of telomerase. Even a mutation of the RNA template of telomerase would render the telomerase unable to extend telomeres, and therefore not be able to grant replicative immortality to cancer, not allow glycolysis to be inititated, and not upregulate Blackburn's 70 cancer genes. Since Blackburn has shown that most of the harmful cancer-related effects of telomerase are dependent on an intact RNA template, it seems a very worthwhile target for drug development. If indeed some cancer stem cells use an alternative method of telomere maintenance, it should be noted that they are still killed when the RNA template of telomerase is blocked. According to Blackburn's opinion at most of her lectures, it is a big mistake to think that telomerase is involved with only extending telomeres. Stopping glycolysis in cancer stem cells and preventing the upregulation of 70 bad genes is probably what is killing cancer stem cells if they are using alternative methods.

See also

- DNA repair

External links

- T.A. Sciences live Q&A Event on Telomere Video on Demand event [34]
- The Telomerase Database - A Web-based tool for telomerase research. [35]
- Three-dimensional model of telomerase [36] at MUN
- Telomeres and Telomerase: Their Implications in Human Health and Disease [37] on-line lecture by Elizabeth Blackburn
- MeSH *Telomerase* [37]
- MD offering Telomerase-based therapies. [38]

References

[1] Olovnikov AM. A theory of marginotomy. The incomplete copying of template margin in enzymic synthesis of polynucleotides and biological significance of the phenomenon. J Theor Biol. 1973 Sep 14;41(1):181-90

[2] Greider, C.W. & Blackburn, E.H. (1985). "Identification of a specific telomere terminal transferase activity in Tetrahymena extracts". *Cell* **43** (2 Pt 1): 405–413. doi: 10.1016/0092-8674(85)90170-9 (http://dx.doi.org/10.1016/0092-8674(85)90170-9). PMID 3907856 (http://www.ncbi.nlm.nih.gov/pubmed/3907856).

[3] http://nobelprize.org/nobel_prizes/medicine/laureates/2009/press.html

[4] Witzany, G. (2008). "The Viral Origins of Telomeres and Telomerases and their Important Role in Eukaryogenesis and Genome Maintenance". *Biosemiotics* **1**: 191–206. doi: 10.1007/s12304-008-9018-0 (http://dx.doi.org/10.1007/s12304-008-9018-0).

[5] Cohen S, Graham M, Lovrecz G, Bache N, Robinson P, Reddel R (2007). "Protein composition of catalytically active human telomerase from immortal cells". *Science* **315** (5820): 1850–3. doi: 10.1126/science.1138596 (http://dx.doi.org/10.1126/science.1138596). PMID 17395830 (http://www.ncbi.nlm.nih.gov/pubmed/17395830).

[6] HUGO Gene Nomenclature Committee(HGNC) (http://www.genenames.org/index.html)- TERT (http://www.genenames.org/data/hgnc_data.php?hgnc_id=11730)

[7] HGNC - TERC (http://www.genenames.org/data/hgnc_data.php?hgnc_id=11727)

[8] HGNC - DKC1 (http://www.genenames.org/data/hgnc_data.php?hgnc_id=2890)

[9] HGNC - TEP1 (http://www.genenames.org/data/hgnc_data.php?hgnc_id=11726)

[10] NCBI - telomerase reverse transcriptase isoform 1 (http://www.ncbi.nlm.nih.gov/protein/109633031)

[11] NCBI - telomerase reverse transcriptase (http://www.ncbi.nlm.nih.gov/sites/entrez?db=protein&cmd=DetailsSearch&term=telomerase+reverse+transcriptase&log$=activity)

[12] Gillis, A. J.; Schuller, A. P. & Skordalakes, E. (2008), "Structure of the Tribolium castaneum telomerase catalytic subunit TERT", *Nature* **455** (7213): 633–637, doi: 10.1038/nature07283 (http://dx.doi.org/10.1038/nature07283)

[13] Gavory G, Farrow M, Balasubramanian S (2002). "Minimum length requirement of the alignment domain of human telomerase RNA to sustain catalytic activity in vitro" (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC137139/?tool=pubmed). *Nucleic Acids Res.* **30** (20): 4470–80. PMID 12384594. .

[14] Hayflick L, Moorhead PS (1961). "The serial cultivation of human diploid cell strains". *Exp Cell Res* **25**: 585–621. PMID 13905659.

[15] Blasco MA. Telomeres and human disease: aging, cancer, and beyond. *Nat Rev Genet.* 2005 Aug;6(8):611-22. PMID 16136653

[16] http://www.smart-publications.com/articles/060116-fossel.php

[17] de Magalhaes JP, Toussain O. Telomeres and telomerase: a modern fountain of youth? Rejuvenation Res. 2004 Summer;7(2):126-33 PMID 15312299

[18] Tomás-Loba A, Flores I, Fernández-Marcos PJ, Cayuela ML, Maraver A, Tejera A, Borrás C, Matheu A, Klatt P, Flores JM, Viña J, Serrano M, Blasco MA. Telomerase reverse transcriptase delays aging in cancer-resistant mice. Cell. 2008 Nov 14;135(4):609-22 PMID 19013273

[19] PR Newswire (2007). *New Product Scientifically Battles Aging at the Cellular Level-Exclusively licensed from the Geron Corporation, TA-65 is the world's first Telomerase Activator* (http://www.lef.org/news/LefDailyNews.htm?NewsID=5216&Section=AGING). Life Extension Magazine. .

[20] Tanglao, Shawna, et al. (2008). *The Discovery of C0057684, a Telomerase Activity Inducing Compound* (http://www.mfoundation.org/UABBA/presenting/abstracts/tanglao/). The Methuselah Foundation. .

[21] Sierra Sciences (2009). *Cure Aging or Die Trying* (http://www.sierrasci.com). . .

[22] Britt, Robert Roy (2009). *One Key Found for Living to 100* (http://www.livescience.com/health/091112-anti-aging-telomeres.html). LiveScience. .

[23] Bryan TM, Englezou A, Gupta J, Bacchetti S, Reddel RR. Telomere elongation in immortal human cells without detectable telomerase activity. *EMBO J.* 1995 Sep 1;14(17):4240-8. PMID 7556065

[24] Henson JD, Neumann AA, Yeager TR, Reddel RR (2002). "Alternative lengthening of telomeres in mammalian cells" (http://www.nature.com/onc/journal/v21/n4/full/1205058a.html). *Oncogene* **21** (4): 598–610. PMID 11850785 (http://www.ncbi.nlm.nih.gov/pubmed/11850785). .

[25] Reuters (2006-07-21), "The poor age faster than the rich: study" (http://www.smh.com.au/news/World/The-poor-age-faster-than-the-rich-study/2006/07/21/1153166552145.html), *Sydney Morning Herald*,

[26] Yamaguchi, H.; Calado, R. T.; Ly, H.; Kajigaya, S.; Baerlocher, G. M.; Chanock, S. J.; Lansdorp, P. M. & Young, N. S. (2005), "Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia", *New England Journal of Medicine* **352** (14): 1413–1424, doi: 10.1056/NEJMoa042980 (http://dx.doi.org/10.1056/NEJMoa042980), PMID 15814878 (http://www.ncbi.nlm.nih.gov/pubmed/15814878)

[27] Zhang, A.; Zheng, C.; Hou, M.; Lindvall, C.; Li, K. J.; Erlandsson, F.; Bjorkholm, M.; Gruber, A. *et al*. (2003), "Deletion of the telomerase reverse transcriptase gene and haploinsufficiency of telomere maintenance in Cri du chat syndrome", *The American Journal of Human Genetics* **72** (4): 940–948, doi: 10.1086/374565 (http://dx.doi.org/10.1086/374565), PMID 12629597 (http://www.ncbi.nlm.nih.gov/pubmed/12629597)

[28] Yamaguchi H (2007). "Mutations of telomerase complex genes linked to bone marrow failures" (http://www.jstage.jst.go.jp/article/jnms/74/3/202/_pdf) (PDF). *J Nippon Med Sch.* **74** (3): 202–9. doi: 10.1272/jnms.74.202 (http://dx.doi.org/10.1272/jnms.74.202). PMID 17625368. .

[29] Heiss NS, Knight SW, Vulliamy TJ *et al.* (1998). "X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions". *Nat Genet.* **19** (1): 32–8. PMID 9590285.

[30] Vulliamy TJ, Walne A, Baskaradas A *et al.* (2005). "Mutations in the reverse transcriptase component of telomerase (TERT) in patients with bone marrow failure". *Blood Cells Mol Dis.* **34** (3): 257–63. PMID 15885610.

[31] Vulliamy T, Marrone A, Goldman F *et al.* (2001). "The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita". *Nature* **413** (6854): 432–5. PMID 11574891.

[32] Marrone, A.; Walne, A. & Dokal, I. (2005), "Dyskeratosis congenita: telomerase, telomeres and anticipation", *Current Opinion in Genetics & Development* **15** (3): 249–257, doi: 10.1016/j.gde.2005.04.004 (http://dx.doi.org/10.1016/j.gde.2005.04.004), PMID 15917199 (http://www.ncbi.nlm.nih.gov/pubmed/15917199)

[33] Armanios, M.; Chen, J. L.; Chang, Y. P.; Brodsky, R. A.; Hawkins, A.; Griffin, C. A.; Eshleman, J. R.; Cohen, A. R. *et al.* (2005), "Haploinsufficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita", *PNAS* **102** (44): 15960–15964, doi: 10.1073/pnas.0508124102 (http://dx.doi.org/10.1073/pnas.0508124102), PMID 16247010 (http://www.ncbi.nlm.nih.gov/pubmed/16247010)

[34] http://www.live.tasciences.com

[35] http://telomerase.asu.edu/

[36] http://www.mun.ca/biochem/courses/3107/images/telomerase_model.gif

[37] http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Telomerase

[38] http://www.telomeraseactivation.org

Telomerase reverse transcriptase

edit
[1]

Telomerase reverse transcriptase	
Identifiers	
Symbols	TERT [2]; EST2; TCS1; TP2; TRT; hEST2
External IDs	OMIM: 187270 [3] MGI: 1202709 [4] HomoloGene: 31141 [5] GeneCards: TERT Gene [6]

Gene ontology	
Molecular function	• DNA binding [7] • telomeric template RNA reverse transcriptase activity [8] • RNA binding [9] • protein binding [10] • transferase activity [11] • telomeric DNA binding [12]
Cellular component	• chromosome, telomeric region [13] • nucleus [14] • chromosome [15] • telomerase holoenzyme complex [16]
Biological process	• telomere maintenance [17] • RNA-dependent DNA replication [18]

RNA expression pattern

More reference expression data [19]

Orthologs		
Species	**Human**	**Mouse**
Entrez	7015 [20]	21752 [21]
Ensembl	ENSG00000164362 [22]	ENSMUSG00000021611 [23]
UniProt	O14746 [24]	A0JNY9 [25]
RefSeq (mRNA)	NM_198253 [26]	NM_009354 [27]
RefSeq (protein)	NP_937983 [28]	NP_033380 [29]
Location (UCSC)	Chr 5: 1.31 - 1.35 Mb [30]	Chr 13: 74.09 - 74.12 Mb [31]

PubMed search	[32]	[33]	

Telomerase reverse transcriptase (abbreviated to **TERT**, or **hTERT** in humans) is a catalytic subunit of the enzyme telomerase.[34] Its absence (usually as a result of a chromosomal mutation) is associated with the disorder Cri du chat.[35] [36]

Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by addition of the telomere repeat TTAGGG. The enzyme consists of a protein component with reverse transcriptase activity, encoded by this gene, and an RNA component which serves as a template for the telomere repeat. Telomerase expression plays a role in cellular senescence, as it is normally repressed in postnatal somatic cells resulting in progressive shortening of telomeres. Deregulation of telomerase expression in somatic cells may be involved in oncogenesis. Studies in mice suggest that telomerase also participates in chromosomal repair, since de novo synthesis of telomere repeats may occur at double-stranded breaks. Alternatively spliced variants encoding different isoforms of telomerase reverse transcriptase have been identified; the full-length sequence of some variants has not been determined. Alternative splicing at this locus is thought to be one mechanism of regulation of telomerase activity.[37]

Interactions

Telomerase reverse transcriptase has been shown to interact with Ku70,[38] YWHAQ,[39] Nucleolin,[40] Ku80,[38] Heat shock protein 90kDa alpha (cytosolic), member A1,[41] [42] MCRS1[43] and PINX1.[44]

Further reading

- Mattson MP, Fu W, Zhang P (2001). "Emerging roles for telomerase in regulating cell differentiation and survival: a neuroscientist's perspective.". *Mech. Ageing Dev.* **122** (7): 659–71. doi:10.1016/S0047-6374(01)00221-4 [45]. PMID 11322991 [46].
- Castillo Ureta H, Barrera Saldaña HA, Martínez Rodríguez HG (2003). "[Telomerase: an enzyme with multiple applications in cancer research]". *Rev. Invest. Clin.* **54** (4): 342–8. PMID 12415959 [47].
- Janknecht R (2004). "On the road to immortality: hTERT upregulation in cancer cells.". *FEBS Lett.* **564** (1-2): 9–13. doi:10.1016/S0014-5793(04)00356-4 [48]. PMID 15094035 [49].
- Cristofari G, Sikora K, Lingner J (2007). "Telomerase unplugged.". *ACS Chem. Biol.* **2** (3): 155–8. doi:10.1021/cb700037c [50]. PMID 17373762 [51].
- Beliveau A, Yaswen P (2007). "Soothing the watchman: telomerase reduces the p53-dependent cellular stress response.". *Cell Cycle* **6** (11): 1284–7. PMID 17534147 [52].
- Bellon M, Nicot C (2007). "Telomerase: a crucial player in HTLV-I-induced human T-cell leukemia.". *Cancer genomics & proteomics* **4** (1): 21–5. PMID 17726237 [53].

See also

- telomerase
- reverse transcriptase

External links

- MeSH *TERT+protein,+human* [54]

References

[1] http://en.wikipedia.org/wiki/Template%3Apbb%2F7015

[2] http://www.genenames.org/data/hgnc_data.php?hgnc_id=11730

[3] http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=187270

[4] http://www.informatics.jax.org/searches/accession_report.cgi?id=MGI:1202709

[5] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=homologene&dopt=HomoloGene&list_uids=31141

[6] http://www.genecards.org/cgi-bin/carddisp.pl?id_type=entrezgene&id=7015

[7] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0003677

[8] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0003721

[9] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0003723

[10] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0005515

[11] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0016740

[12] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0042162

[13] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0000781

[14] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0005634

[15] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0005694

[16] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0005697

[17] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0000723

[18] http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?view=details&search_constraint=terms&depth=0&query=GO:0006278

[19] http://biogps.gnf.org/gene/7015/

[20] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=retrieve&dopt=default&list_uids=7015&rn=1

[21] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=retrieve&dopt=default&list_uids=21752&rn=1

[22] http://www.ensembl.org/Homo_sapiens/geneview?gene=ENSG00000164362;db=core

[23] http://www.ensembl.org/Mus_musculus/geneview?gene=ENSMUSG00000021611;db=core

[24] http://www.uniprot.org/uniprot/O14746

[25] http://www.uniprot.org/uniprot/A0JNY9

[26] http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NM_198253

[27] http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NM_009354

[28] http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NP_937983

[29] http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NP_033380

[30] http://genome.ucsc.edu/cgi-bin/hgTracks?org=Human&db=hg18&position=chr5:1306282-1348162

[31] http://genome.ucsc.edu/cgi-bin/hgTracks?org=Mouse&db=mm8&position=chr13:74092992-74115843

[32] http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Link&LinkName=gene_pubmed&from_uid=7015

[33] http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Link&LinkName=gene_pubmed&from_uid=21752

[34] Kirkpatrick KL, Mokbel K (2001). "The significance of human telomerase reverse transcriptase (hTERT) in cancer". *Eur J Surg Oncol* **27** (8): 754–60. doi: 10.1053/ejso.2001.1151 (http://dx.doi.org/10.1053/ejso.2001.1151). PMID 11735173 (http://www.ncbi.nlm.nih. gov/pubmed/11735173).

[35] Zhang A, Zheng C, Hou M, Lindvall C, Li KJ, Erlandsson F, Björkholm M, Gruber A, Blennow E, Xu D (2003). "Deletion of the telomerase reverse transcriptase gene and haploinsufficiency of telomere maintenance in Cri du chat syndrome" (http://www.pubmedcentral. nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=12629597). *Am. J. Hum. Genet.* **72** (4): 940–8. doi: 10.1086/374565 (http://dx.doi. org/10.1086/374565). PMID 12629597 (http://www.ncbi.nlm.nih.gov/pubmed/12629597). .

[36] Cerruti Mainardi P (2006). "Cri du Chat syndrome". *Orphanet J Rare Dis* **1**: 33. doi: 10.1186/1750-1172-1-33 (http://dx.doi.org/10. 1186/1750-1172-1-33). PMID 16953888 (http://www.ncbi.nlm.nih.gov/pubmed/16953888).

[37] "Entrez Gene: TERT telomerase reverse transcriptase" (http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView& TermToSearch=7015). .

[38] Chai, Weihang; Ford Lance P, Lenertz Lisa, Wright Woodring E, Shay Jerry W (Dec. 2002). "Human Ku70/80 associates physically with telomerase through interaction with hTERT". *J. Biol. Chem.* (United States) **277** (49): 47242–7. doi: 10.1074/jbc.M208542200 (http://dx. doi.org/10.1074/jbc.M208542200). ISSN 0021-9258 (http://worldcat.org/issn/0021-9258). PMID 12377759 (http://www.ncbi.nlm.

nih.gov/pubmed/12377759).

[39] Seimiya, H; Sawada H, Muramatsu Y, Shimizu M, Ohko K, Yamane K, Tsuruo T (Jun. 2000). "Involvement of 14-3-3 proteins in nuclear localization of telomerase". *EMBO J.* (ENGLAND) **19** (11): 2652–61. doi: 10.1093/emboj/19.11.2652 (http://dx.doi.org/10.1093/emboj/19.11.2652). ISSN 0261-4189 (http://worldcat.org/issn/0261-4189). PMID 10835362 (http://www.ncbi.nlm.nih.gov/pubmed/10835362).

[40] Khurts, Shilagardi; Masutomi Kenkichi, Delgermaa Luvsanjav, Arai Kuniaki, Oishi Naoki, Mizuno Hideki, Hayashi Naoyuki, Hahn William C, Murakami Seishi (Dec. 2004). "Nucleolin interacts with telomerase". *J. Biol. Chem.* (United States) **279** (49): 51508–15. doi: 10.1074/jbc.M407643200 (http://dx.doi.org/10.1074/jbc.M407643200). ISSN 0021-9258 (http://worldcat.org/issn/0021-9258). PMID 15371412 (http://www.ncbi.nlm.nih.gov/pubmed/15371412).

[41] Haendeler, Judith; Hoffmann Jörg, Rahman Sandy, Zeiher Andreas M, Dimmeler Stefanie (Feb. 2003). "Regulation of telomerase activity and anti-apoptotic function by protein-protein interaction and phosphorylation". *FEBS Lett.* (Netherlands) **536** (1-3): 180–6. doi: 10.1016/S0014-5793(03)00058-9 (http://dx.doi.org/10.1016/S0014-5793(03)00058-9). ISSN 0014-5793 (http://worldcat.org/issn/0014-5793). PMID 12586360 (http://www.ncbi.nlm.nih.gov/pubmed/12586360).

[42] Kawauchi, Kiyotaka; Ihjima Kimiko, Yamada Osamu (May. 2005). "IL-2 increases human telomerase reverse transcriptase activity transcriptionally and posttranslationally through phosphatidylinositol 3'-kinase/Akt, heat shock protein 90, and mammalian target of rapamycin in transformed NK cells". *J. Immunol.* (United States) **174** (9): 5261–9. ISSN 0022-1767 (http://worldcat.org/issn/0022-1767). PMID 15843522 (http://www.ncbi.nlm.nih.gov/pubmed/15843522).

[43] Song, Hai; Li Yiliang, Chen Guoyuan, Xing Zhen, Zhao Jing, Yokoyama Kazunari K, Li Tsaiping, Zhao Mujun (Apr. 2004). "Human MCRS2, a cell-cycle-dependent protein, associates with LPTS/PinX1 and reduces the telomere length". *Biochem. Biophys. Res. Commun.* (United States) **316** (4): 1116–23. doi: 10.1016/j.bbrc.2004.02.166 (http://dx.doi.org/10.1016/j.bbrc.2004.02.166). ISSN 0006-291X (http://worldcat.org/issn/0006-291X). PMID 15044100 (http://www.ncbi.nlm.nih.gov/pubmed/15044100).

[44] Zhou, X Z; Lu K P (Nov. 2001). "The Pin2/TRF1-interacting protein PinX1 is a potent telomerase inhibitor". *Cell* (United States) **107** (3): 347–59. doi: 10.1016/S0092-8674(01)00538-4 (http://dx.doi.org/10.1016/S0092-8674(01)00538-4). ISSN 0092-8674 (http://worldcat.org/issn/0092-8674). PMID 11701125 (http://www.ncbi.nlm.nih.gov/pubmed/11701125).

[45] http://dx.doi.org/10.1016%2FS0047-6374%2801%2900221-4

[46] http://www.ncbi.nlm.nih.gov/pubmed/11322991

[47] http://www.ncbi.nlm.nih.gov/pubmed/12415959

[48] http://dx.doi.org/10.1016%2FS0014-5793%2804%2900356-4

[49] http://www.ncbi.nlm.nih.gov/pubmed/15094035

[50] http://dx.doi.org/10.1021%2Fcb700037c

[51] http://www.ncbi.nlm.nih.gov/pubmed/17373762

[52] http://www.ncbi.nlm.nih.gov/pubmed/17534147

[53] http://www.ncbi.nlm.nih.gov/pubmed/17726237

[54] http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=TERT+protein,+human

DNA computing

DNA computing is a form of computing which uses DNA, biochemistry and molecular biology, instead of the traditional silicon-based computer technologies. DNA computing, or, more generally, molecular computing, is a fast developing interdisciplinary area. Research and development in this area concerns theory, experiments and applications of DNA computing.

History

This field was initially developed by Leonard Adleman of the University of Southern California, in 1994.[1] Adleman demonstrated a proof-of-concept use of DNA as a form of computation which solved the seven-point Hamiltonian path problem. Since the initial Adleman experiments, advances have been made and various Turing machines have been proven to be constructible.[2] [3]

In 2002, researchers from the Weizmann Institute of Science in Rehovot, Israel, unveiled a programmable molecular computing machine composed of enzymes and DNA molecules instead of silicon microchips.[4] On April 28, 2004, Ehud Shapiro, Yaakov Benenson, Binyamin Gil, Uri Ben-Dor, and Rivka Adar at the Weizmann Institute announced in the journal Nature that they had constructed a DNA computer.[5] This was coupled with an input and output module and is capable of diagnosing cancerous activity within a cell, and then releasing an anti-cancer drug upon diagnosis.

Capabilities

DNA computing is fundamentally similar to parallel computing in that it takes advantage of the many different molecules of DNA to try many different possibilities at once. [6]

DNA computing also offers much lower power consumption than traditional silicon computers. DNA uses adenosine triphosphate (ATP) as fuel to allow ligation or as a means to heat the strand to cause disassociation. [7] Both strand hybridization and the hydrolysis of the DNA backbone can occur spontaneously, powered by the potential energy stored in DNA. Consumption of two ATP molecules releases 1.5×10^{-19} J. Even with a large number of transitions per second using two ATP molecules, power output is still low. For instance, Kahan reports 109 transitions per second with an energy consumption of 10^{-10} W,[8] and similarly Shapiro reports a system producing 7.5×10^{11} outputs in 4000 sec resulting in an energy consumption rate of $\sim 10^{-10}$ W.[9]

For certain specialized problems, DNA computers are faster and smaller than any other computer built so far. But DNA computing does not provide any new capabilities from the standpoint of computability theory, the study of which problems are computationally solvable using different models of computation. For example, if the space required for the solution of a problem grows exponentially with the size of the problem (EXPSPACE problems) on von Neumann machines, it still grows exponentially with the size of the problem on DNA machines. For very large EXPSPACE problems, the amount of DNA required is too large to be practical. (Quantum computing, on the other hand, *does* provide some interesting new capabilities).

DNA computing overlaps with, but is distinct from, DNA nanotechnology. The latter uses the specificity of Watson-Crick basepairing and other DNA properties to make novel structures out of DNA. These structures can be used for DNA computing, but they do not have to be. Additionally, DNA computing can be done without using the types of molecules made possible by DNA nanotechnology.

Methods

There are multiple methods for building a computing device based on DNA, each with its own advantages and disadvantages. Most of these build the basic logic gates (AND, OR, NOT) associated with digital logic from a DNA basis. Some of the different bases include DNAzymes, deoxyoligonucleotides, enzymes, DNA tiling, and polymerase chain reaction.

DNAzymes

Catalytic DNA (deoxyribozyme or DNAzyme) catalyze a reaction when interacting with the appropriate input, such as a matching oligonucleotide. These DNAzymes are used to build logic gates analogous to digital logic in silicon; however, DNAzymes are limited to 1-, 2-, and 3-input gates with no current implementation for evaluating statements in series.

The DNAzyme logic gate changes its structure when it binds to a matching oligonucleotide and the fluorogenic substrate it is bonded to is cleaved free. While other materials can be used, most models use a fluorescence-based substrate because it is very easy to detect, even at the single molecule limit.[10] The amount of fluorescence can then be measured to tell whether or not a reaction took place. The DNAzyme that changes is then "used," and cannot initiate any more reactions. Because of this, these reactions take place in a device such as a continuous stirred-tank reactor, where old product is removed and new molecules added.

Two commonly used DNAzymes are named E6 and 8-17. These are popular because they allow cleaving of a substrate in any arbitrary location.[11] Stojanovic and MacDonald have used the E6 DNAzymes to build the MAYA I[12] and MAYA II[13] machines, respectively; Stojanovic has also demonstrated logic gates using the 8-17 DNAzyme.[14] While these DNAzymes have been demonstrated to be useful for constructing logic gates, they are limited by the need for a metal cofactor to function, such as Zn^{2+} or Mn^{2+}, and thus are not useful in vivo.[10] [15]

Enzymes

Enzyme based DNA computers are usually of the form of a simple Turing machine; there is analogous hardware, in the form of an enzyme, and software, in the form of DNA. [16]

Shapiro has demonstrated a DNA computer using the FokI enzyme[17] and expanded on his work by going on to show automata that diagnose and react to prostate cancer: under expression of the genes PPAP2B and GSTP1 and an over expression of PIM1 and HPN.[5] His automata evaluated the expression of each gene, one gene at a time, and on positive diagnosis then released a single strand DNA molecule (ssDNA) that is an antisense for MDM2. MDM2 is a repressor of protein 53, which itself is a tumor suppressor.[18] On negative diagnosis it was decided to release a suppressor of the positive diagnosis drug instead of doing nothing. A limitation of this implementation is that two separate automata are required, one to administer each drug. The entire process of evaluation until drug release took around an hour to complete. This method also requires transition molecules as well as the FokI enzyme to be present. The requirement for the FokI enzyme limits application *in vivo*, at least for use in "cells of higher organisms".[19] It should also be pointed out that the 'software' molecules can be reused in this case.

Examples

- MAYA II
- Computational Genes

See also

- Biocomputers
- Computational gene
- Molecular electronics
- Peptide computing
- Parallel computing
- Quantum computing

Further reading

- Martyn Amos (June 2005). *Theoretical and Experimental DNA Computation* [20]. Springer. ISBN 3-540-65773-8. — The first general text to cover the whole field.
- Gheorge Paun, Grzegorz Rozenberg, Arto Salomaa (October 1998). *DNA Computing - New Computing Paradigms*. Springer-Verlag. ISBN 3-540-64196-3. — The book starts with an introduction to DNA-related matters, the basics of biochemistry and language and computation theory, and progresses to the advanced mathematical theory of DNA computing.
- JB. Waldner (January 2007). *Nanocomputers and Swarm Intelligence*. ISTE. pp. 189. ISBN 2746215160.

External links

- How Stuff Works explanation [21]
- Physics Web [22]
- Ars Technica [23]
- NY Times DNA Computer for detecting Cancer [24]
- Bringing DNA computers to life, in Scientific American [25]
- Japanese Researchers store information in bacteria DNA [26]
- International Meeting on DNA Computing and Molecular Programming [27]

References

[1] Leonard M. Adleman (1994-11-11). "Molecular Computation Of Solutions To Combinatorial Problems" (http://www.usc.edu/dept/ molecular-science/papers/fp-sci94.pdf). *Science* **266** (11): 1021−1024. doi: 10.1126/science.7973651 (http://dx.doi.org/10.1126/science. 7973651). . — The first DNA computing paper. Describes a solution for the directed Hamiltonian path problem.

[2] Dan Boneh, Christopher Dunworth, Richard J. Lipton, and Jiri Sgall (1996). "On the Computational Power of DNA" (http://www.dna. caltech.edu/courses/cs191/paperscs191/bonehetal.pdf). *DAMATH: Discrete Applied Mathematics and Combinatorial Operations Research and Computer Science* **71**. . — Describes a solution for the boolean satisfiability problem.

[3] Lila Kari, Greg Gloor, Sheng Yu (January 2000). "Using DNA to solve the Bounded Post Correspondence Problem" (http://citeseer.ist.psu. edu/kari00using.html). *Theoretical Computer Science* **231** (2): 192−203. . — Describes a solution for the bounded Post correspondence problem, a hard-on-average NP-complete problem.

[4] Lovgren, Stefan (2003-2-24). "Computer Made from DNA and Enzymes" (http://news.nationalgeographic.com/news/2003/02/ 0224_030224_DNAcomputer.html). *National Geographic*. . Retrieved 2009-11-26.

[5] Yaakov Benenson1, Binyamin Gil, Uri Ben-Dor, Rivka Adar, Ehud Shapiro (2004-04-28). "An autonomous molecular computer for logical control of gene expression" (http://www.wisdom.weizmann.ac.il/~lbn/other_links/ShapiroNature2004.pdf). *Nature* **429**: 423−429. doi: 10.1038/nature02551 (http://dx.doi.org/10.1038/nature02551). .

[6] David I. Lewin (2002). "DNA Computing". *Computing in Science & Engineering* **4** (3): 5−8. doi: 10.1109/5992.998634 (http://dx.doi.org/ 10.1109/5992.998634).

[7] C. H. Bennett (1973). "Logical Reversal of Computation". *IBM Journal of Research and Development* **17** (6): 525−532.

[8] Maya Kahan (2008). "Towards Molecular Computers that Operate in a Biological Environment". *Physica D: Nonlinear Phenomena* **237** (9): 1165–1172. doi: 10.1016/j.physd.2008.01.027 (http://dx.doi.org/10.1016/j.physd.2008.01.027).

[9] Ehud Shapiro (2004). "Programmable and Autonomous Computing Machine Made of Biomolecules". *Nature* **414** (6862): 430–434. doi: 10.1038/35106533 (http://dx.doi.org/10.1038/35106533).

[10] Shimon Weiss (1999). "Fluorescence Spectroscopy of Single Biomolecules". *Science* **283** (5408): 1676–1683. doi: 10.1126/science.283.5408.1676 (http://dx.doi.org/10.1126/science.283.5408.1676).

[11] Stephen W. Santoro, Gerald F. Joyce (1997). "A General Purpose RNA-cleaving DNA Enzyme". *Proc. Natl. Acad. Sci.* **94** (9): 4262–4266. doi: 10.1073/pnas.94.9.4262 (http://dx.doi.org/10.1073/pnas.94.9.4262).

[12] Milan Stojanovic, Darko Stefanovic (2003). "A Deoxyribozyme-Based Molecular Automaton". *Nature Biotechnology* **21** (9): 1069–1074. doi: 10.1038/nbt862 (http://dx.doi.org/10.1038/nbt862).

[13] Joanne MacDonald, et al. (2006). "Medium Scale Integration of Molecular Logic Gates in an Automaton". *Nano Letters* **6** (11): 2598–2603. doi: 10.1021/nl0620684 (http://dx.doi.org/10.1021/nl0620684).

[14] Milan Stojanovic, et al. (2002). "Deoxyribozyme-Based Logic Gates". *Journal of the American Chemical Society* **124**: 3555–3561. doi: 10.1021/ja016756v (http://dx.doi.org/10.1021/ja016756v).

[15] Rani P. G. Cruz, Johanna B. Withers, Yingfu Li. (2004). "Dinucleotide Junction Cleavage: Versatility of 8-17 Deoxyribozyme". *Chemistry & Biology* **11** (1): 57–67.

[16] Shapiro, Ehud (1999-12-07). "A Mechanical Turing Machine: Blueprint for a Biomolecular Computer" (http://www.wisdom.weizmann.ac.il/~udi/DNA5/scripps_short/index.htm). Weizmann Institute of Science. . Retrieved 2009-08-13.

[17] Ehud Shapiro, et al. (2001). "Programmable and Autonomous Computing Machine Made of Biomolecules". *Nature* **414** (6862): 430–434. doi: 10.1038/35106533 (http://dx.doi.org/10.1038/35106533).

[18] Gareth L. Bond, Wenwei Hu, and Arnold J. Levine (2005). "MDM2 is a Central Node in the p53 Pathway: 12 Years and Counting". *Current Cancer Drug Targets* **5** (1): 3–8. doi: 10.2174/1568009053332627 (http://dx.doi.org/10.2174/1568009053332627).

[19] Maya Kahan, et al. (2008). "Towards Molecular Computers that Operate in a Biological Environment". *Physica D: Nonlinear Phenomen* **237** (9): 1165–1172.

[20] http://www.springeronline.com/sgw/cda/frontpage/0,11855,3-0-22-1995351-0,00.html

[21] http://computer.howstuffworks.com/dna-computer.htm

[22] http://physicsweb.org/article/news/6/3/11

[23] http://www.arstechnica.com/reviews/2q00/dna/dna-1.html

[24] http://www.nytimes.com/2004/04/29/science/29DNA.html

[25] http://www.sciam.com/article.cfm?articleID=0005BC6A-97DF-1446-951483414B7F0101

[26] http://www.tfot.info/index.php?option=com_rsgallery2&page=inline&id=197&catid=1&limitstart=177

[27] http://www.dna-computing.org

DNA nanotechnology

Part of a series of articles on
Molecular self-assembly
Self-assembled monolayer   Supramolecular assembly   DNA nanotechnology
See also   Nanotechnology

DNA nanotechnology is a subfield of nanotechnology which seeks to use the unique molecular recognition properties of DNA and other nucleic acids to create novel, controllable structures out of DNA. The DNA is thus used as a structural material rather than as a carrier of genetic information, making it an example of bionanotechnology. This has possible applications in molecular self-assembly and in DNA computing.

DNA nanotechnology is that branch of one,which deals with the study and application of molecular recognition properties of DNA and other nucleic acids to create controllable structures out of them for computing and assembly.

Introduction: DNA crossover molecules
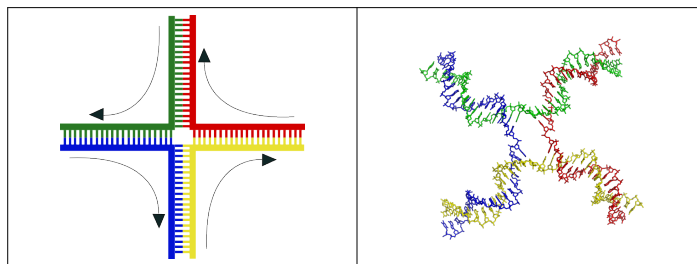
Structure of the 4-arm junction.
Left: A schematic. **Right**: A more realistic model.[1]
Each of the four separate DNA single strands are shown in different colors.

DNA nanotechnology makes use of branched DNA structures to create DNA complexes with useful properties. DNA is normally a linear molecule, in that its axis is unbranched. However, DNA molecules containing junctions can also be made. For example, a four-arm junction can be made using four individual DNA strands which are complementary to each other in the correct pattern. Due to Watson-Crick base pairing, only portions of the strands which are complementary to each other will attach to each other to form duplex DNA. This four-arm junction is an immobile form of a Holliday junction.

Junctions can be used in more complex molecules. The most important of these is the "double-crossover" or DX motif. Here, two DNA duplexes lie next to each other, and share two junction points where strands cross from one duplex into the other. This molecule has the advantage that the junction points are now constrained to a single orientation as opposed to being flexible as in the four-arm junction. This makes the DX motif suitible as a structural building block for larger DNA complexes.[3]

A double-crossover (DX) molecule. This molecule consists of five DNA single strands which form two double-helical domains, on the left and the right in this image. There are two crossover points where the strands cross from one domain into the other. Image from Mao, 2004. [2]

Tile-based arrays

Assembly of a DX array. Each bar represents a double-helical domain of DNA, with the shapes representing complimentary sticky ends. The DX molecule at top will combine into the two-dimensional DNA array shown at bottom. Image from Mao, 2004. [2]

DX arrays

DX, Double , molecules can be equipped with sticky ends in order to combine them into a two-dimenstional periodic lattice. Each DX molecule has four termini, one at each end of the two double-helical domains, and these can be equipped with sticky ends that program them to combine into a specific pattern. More than one type of DX can be used which can be made to arrange in rows or any other tessellated pattern. They thus form extended flat sheets which are essentially two-dimensional crystals of DNA.[4]

DNA nanotubes

In addition to flat sheets, DX arrays have been made to form hollow tubes of 4-20 nm diameter. These DNA nanotubes are somewhat similar in size and shape to carbon nanotubes, but the

carbon nanotubes are stronger and better conductors, whereas the DNA nanotubes are more easily modified and connected to other structures.[5]

Other tile arrays

Two-dimensional arrays have been made out of other motifs as well, including the Holliday junction rhombus array as well as various DX-based arrays in the shapes of triangles and hexagons.[6] Another motif, the six-helix bundle, has the ability to form three-dimensional DNA arrays as well.[7]

DNA origami

An alternative to the tile-based approach, two-dimensional DNA structures can be made from a single, long DNA strand of arbitrary sequence which is folded into the desired shape by using shorter, "staple" strands. This allows the creation of two-dimensional shapes at the nanoscale using DNA. Demonstrated designs have included the smiley face and a coarse map of North America. DNA origami was the cover story of *Nature* on March 15, 2006.[8]

DNA polyhedra

A number of three-dimensional DNA molecules have been made which have the connectivity of a polyhedron such as an octahedron or cube. In other words, the DNA duplexes trace the edges of a polyhedron with a DNA junction at each vertex. The earliest demonstrations of DNA polyhedra involved multiple ligations and solid-phase synthesis steps to create catenated polyhedra. More recently, there have been demonstrations of a DNA truncated octahedron made from a long single strand designed to fold into the correct conformation, as well as a tetrahedron which can be produced from four DNA strands in a single step.[9]

DNA nanomechanical devices

DNA complexes have been made which change their conformation upon some stimulus. These are intended to have applications in nanorobotics. One of the first such devices, called "molecular tweezers," changes from an open to a closed state based upon the presence of control strands.

DNA machines have also been made which show a twisting motion. One of these makes use of the transition between the B-DNA and Z-DNA forms to respond to a change in buffer conditions. Another relies on the presence of control strands to switch from a paranemic-crossover (PX) conformation to a double-junction (JX2) conformation.[10]

Stem Loop Controllers

A design called a *stem loop*, consisting of a single strand of DNA which has a loop at an end, are a dynamic structure that opens and closes when a piece of DNA bonds to the loop part. This effect has been exploited to create several logic gates. [11] [12] These logic gates have been used to create the computers MAYA I and MAYA II which can play tick-tac-toe to some extent.[13]

Applications

Algorithmic self-assembly

DNA nanotechnology has been applied to the related field of DNA computing. A DX array has been demonstrated whose assembly encodes an XOR operation, which allows the DNA array to implement a cellular automaton which generates a fractal called the Sierpinski gasket. This shows that computation can be incorporated into the assembly of DNA arrays, increasing its scope beyond simple periodic arrays.

Note that DNA computing overlaps with, but is distinct from, DNA nanotechnology. The latter uses the specificity of Watson-Crick basepairing to make novel structures out of DNA. These structures can be used for DNA computing, but they do not have to be. Additionally, DNA computing can be done without using the types of molecules made possible by DNA Nanotechnology.[15]

Nanoarchitecture

The idea of using DNA arrays to template the assembly of other functional molecules has been around for a while, but only recently has progress been made in reducing these kinds of schemes to practice. In 2006, researchers covalently attached gold nanoparticles to a DX-based tile and showed that self-assembly of the DNA structures also assembled the nanoparticles hosted on them. A non-covalent hosting scheme was shown in 2007, using Dervan polyamides on a DX array to arrange streptavidin proteins on specific kinds of tiles on the DNA array.[16] Previously in 2006 LaBean demonstrated the letters "D" "N" and "A" created on a 4x4 DX array using streptavidin. [17]

The Sierpinski gasket.
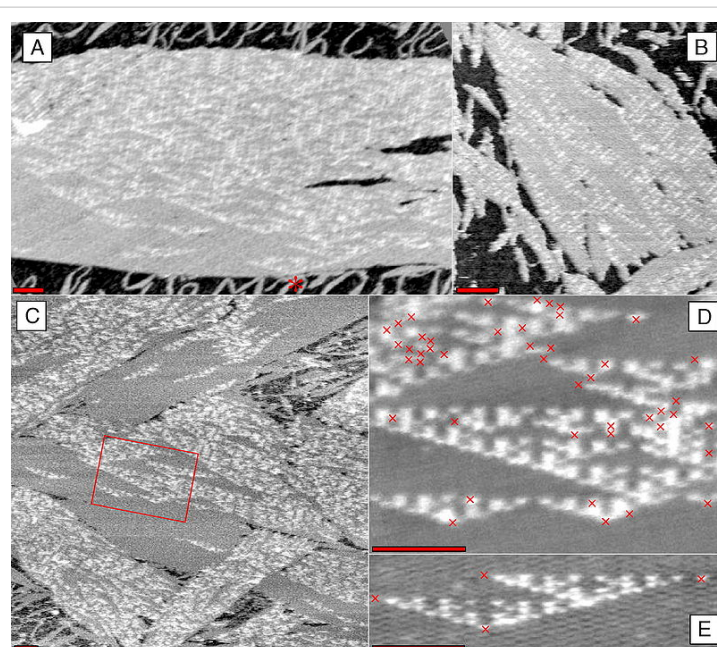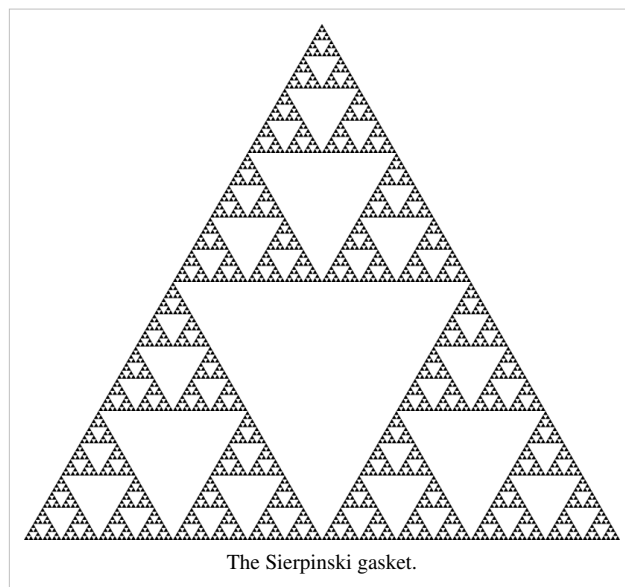
DNA arrays that display a representation of the Sierpinski gasket on their surfaces. Click the image for further details. Image from Rothemund *et al.*, 2004. [14]

DNA has also been used to assemble a single walled carbon nanotube Field-effect transistor.[18]

See also

- Mechanical properties of DNA

External links

- Nanohedron.com [19] images of DNA self assemblies
- Jørgen Kjems lab at Aarhus University [20]
- Thom LaBean lab at Duke University [21]
- Dan Luo lab at Cornell University [22]
- Chengde Mao page at Purdue University [23]
- John Reif lab at Duke University [24]
- Nadrian Seeman lab at NYU [25]
- William M. Shih lab at Harvard Medical School [26]
- Andrew Turberfield lab at Oxford University [27]
- Erik Winfree lab at Caltech [28]
- Hao Yan lab at Arizona State University [29]
- Bernard Yurke formerly at Bell Labs [30] now at Boise State University [31]
- Software for 3D DNA design, modeling and/or simulation:
  - Ascalaph Designer [32]
  - caDNAno [33]
  - GIDEON [34]
  - NanoEngineer-1 [35]
- International Society for Nanoscale Science, Computation and Engineering [36]

References

Note: Click on the doi to access the text of the referenced article.

[1] Created from PDB 1M6G (http://www.rcsb.org/pdb/explore/explore.do?structureId=1M6G)

[2] http://dx.doi.org/10.1371/journal.pbio.0020431

- Seeman, Nadrian C. (1 November 1999). "DNA Engineering and its Application to Nanotechnology". *Trends in Biotechnology* **17** (11): 437–443. doi: 10.1016/S0167-7799(99)01360-8 (http://dx.doi.org/10.1016/S0167-7799(99)01360-8). ISSN 0167-7799 (http://worldcat.org/issn/0167-7799).

- Seeman, Nadrian C. (January 2001). "DNA Nicks and Nodes and Nanotechnology". *Nano Letters* **1** (1): 22–26. doi: 10.1021/nl000182v (http://dx.doi.org/10.1021/nl000182v). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).

- Mao, Chengde (December 2004). "The Emergence of Complexity: Lessons from DNA". *PLoS Biology* **2** (12): 2036–2038. doi: 10.1371/journal.pbio.0020431 (http://dx.doi.org/10.1371/journal.pbio.0020431). ISSN 1544-9173 (http://worldcat.org/issn/1544-9173).

- Kumara, Mudalige T. (July 2008). "Assembly pathway analysis of DNA nanostructures and the construction of parallel motifs". *Nano Letters* **8** (7): 1971–1977. doi: 10.1021/nl800907y (http://dx.doi.org/10.1021/nl800907y). ISSN .

- Winfree, Erik; Liu, Furong; Wenzler, Lisa A. & Seeman, Nadrian C. (6 August 1998). "Design and self-assembly of two-dimensional DNA crystals". *Nature* **394**: 529–544. doi: 10.1038/28998 (http://dx.doi.org/10.1038/28998). ISSN 0028-0836 (http://worldcat.org/issn/0028-0836).

- Liu, Furong; Sha, Ruojie & Seeman, Nadrian C. (10 February 1999). "Modifying the Surface Features of Two-Dimensional DNA Crystals". *Journal of the American Chemical Society* **121** (5): 917–922. doi: 10.1021/ja982824a (http://dx.doi.org/10.1021/ja982824a). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).

- Rothemund, Paul W. K.; Ekani-Nkodo, Axel; Papadakis, Nick; Kumar, Ashish; Fygenson, Deborah Kuchnir & Winfree, Erik (22 December 2004). "Design and Characterization of Programmable DNA Nanotubes". *Journal of the American Chemical Society* **126** (50): 16344–16352. doi: 10.1021/ja044319l (http://dx.doi.org/10.1021/ja044319l). ISSN 0002-7863 (http://worldcat.org/issn/

0002-7863).

- Mao, Chengde; Sun, Weiqiong & Seeman, Nadrian C. (16 June 1999). "Designed Two-Dimensional DNA Holliday Junction Arrays Visualized by Atomic Force Microscopy". *Journal of the American Chemical Society* **121** (23): 5437–5443. doi: 10.1021/ja9900398 (http://dx.doi.org/10.1021/ja9900398). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).

- Constantinou, Pamela E.; Wang, Tong; Kopatsch, Jens; Israel, Lisa B.; Zhang, Xiaoping; Ding, Baoquan; Sherman, William B.; Wang, Xing; Zheng, Jianping; Sha, Ruojie & Seeman, Nadrian C. (2006). "Double cohesion in structural DNA nanotechnology". *Organic and Biomolecular Chemistry* **4**: 3414–3419. doi: 10.1039/b605212f (http://dx.doi.org/10.1039/b605212f).

- Mathieu, Frederick; Liao, Shiping; Kopatsch, Jens; Wang, Tong; Mao, Chengde & Seeman, Nadrian C. (April 2005). "Six-Helix Bundles Designed from DNA". *Nano Letters* **5** (4): 661–665. doi: 10.1021/nl050084f (http://dx.doi.org/10.1021/nl050084f). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).

- Rothemund, Paul W. K. (2006). "Folding DNA to create nanoscale shapes and patterns". *Nature* **440**: 297–302. doi: 10.1038/nature04586 (http://dx.doi.org/10.1038/nature04586). ISSN 0028-0836 (http://worldcat.org/issn/0028-0836).

- Zhang, Yuwen; Seeman, Nadrian C. (1994). "Construction of a DNA-truncated octahedron". *Journal of the American Chemical Society* **116** (5): 1661–1669. doi: 10.1021/ja00084a006 (http://dx.doi.org/10.1021/ja00084a006). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).

- Shih, William M.; Quispe, Joel D.; Joyce, Gerald F. (12 February 2004). "A 1.7-kilobase single-stranded DNA that folds into a nanoscale octahedron". *Nature* **427**: 618–621. doi: 10.1038/nature02307 (http://dx.doi.org/10.1038/nature02307). ISSN 0028-0836 (http://worldcat.org/issn/0028-0836).

- Goodman, R.P.; Schaap, I.A.T.; Tardin, C.F.; Erben, C.M.; Berry, R.M.; Schmidt, C.F.; Turberfield, A.J. (9 December 2005). "Rapid chiral assembly of rigid DNA building blocks for molecular nanofabrication". *Science* **310** (5754): 1661–1665. doi: 10.1126/science.1120367 (http://dx.doi.org/10.1126/science.1120367). ISSN 0036-8075 (http://worldcat.org/issn/0036-8075).

- Yurke, Bernard; Turberfield, Andrew J.; Mills, Allen P., Jr; Simmel, Friedrich C. & Neumann, Jennifer L. (10 August 2000). "A DNA-fuelled molecular machine made of DNA". *Nature* **406**: 605–609. doi: 10.1038/35020524 (http://dx.doi.org/10.1038/35020524). ISSN 0028-0836 (http://worldcat.org/issn/0028-0836).

- Mao, Chengde; Sun, Weiqiong; Shen, Zhiyong & Seeman, Nadrian C. (14 January 1999). "A DNA Nanomechanical Device Based on the B-Z Transition". *Nature* **397**: 144–146. doi: 10.1038/16437 (http://dx.doi.org/10.1038/16437). ISSN .

- Yan, Hao; Zhang, Xiaoping; Shen, Zhiyong & Seeman, Nadrian C. (3 January 2002). "A robust DNA mechanical device controlled by hybridization topology". *Nature* **415**: 62–65. doi: 10.1038/415062a (http://dx.doi.org/10.1038/415062a). ISSN .

[11] DNA Logic Gates (https://digamma.cs.unm.edu/wiki/bin/view/McogPublicWeb/MolecularLogicGates)

[12] (http://www.duke.edu/~jme17/Joshua_E._Mendoza-Elias/Research_Ideas.html)

[13] MAYA II (https://digamma.cs.unm.edu/wiki/bin/view/McogPublicWeb/MolecularAutomataMAYAII)

[14] http://dx.doi.org/10.1371/journal.pbio.0020424

- Rothemund, Paul W. K.; Papadakis, Nick & Winfree, Erik (December 2004). "Algorithmic Self-Assembly of DNA Sierpinski Triangles". *PLoS Biology* **2** (12): 2041–2053. doi: 10.1371/journal.pbio.0020424 (http://dx.doi.org/10.1371/journal.pbio.0020424). ISSN 1544-9173 (http://worldcat.org/issn/1544-9173).

- Robinson, Bruche H.; Seeman, Nadrian C. (August 1987). "The Design of a Biochip: A Self-Assembling Molecular-Scale Memory Device". *Protein Engineering* **1** (4): 295–300. ISSN 0269-2139 (http://worldcat.org/issn/0269-2139). Link (http://peds.oxfordjournals.org/cgi/content/abstract/1/4/295)

- Zheng, Jiwen; Constantinou, Pamela E.; Micheel, Christine; Alivisatos, A. Paul; Kiehl, Richard A. & Seeman Nadrian C. (2006). "2D Nanoparticle Arrays Show the Organizational Power of Robust DNA Motifs". *Nano Letters* **6**: 1502–1504. doi: 10.1021/nl060994c (http://dx.doi.org/10.1021/nl060994c). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).

- Cohen, Justin D.; Sadowski, John P.; Dervan, Peter B. (2007). "Addressing Single Molecules on DNA Nanostructures". *Angewandte Chemie* **46** (42): 7956–7959. doi: 10.1002/anie.200702767 (http://dx.doi.org/10.1002/anie.200702767). ISSN 0570-0833 (http://worldcat.org/issn/0570-0833).

[17] Park, Sung Ha; Sung Ha Park, Constantin Pistol, Sang Jung Ahn, John H. Reif, Alvin R. Lebeck, Chris Dwyer, Thomas H. LaBean (October 2006). "Finite-Size, Fully Addressable DNA Tile Lattices Formed by Hierarchical Assembly Procedures" (http://www3.interscience.wiley.com/journal/113390879/abstract). *Angewandte Chemie* **118** (40): 749–753. doi: 10.1002/ange.200690141 (http://dx.doi.org/10.1002/ange.200690141). ISSN 1521-3757 (http://worldcat.org/issn/1521-3757). .

[18] Keren, K.; Kinneret Keren, Rotem S. Berman, Evgeny Buchstab, Uri Sivan, Erez Braun (November 2003). "DNA-Templated Carbon Nanotube Field-Effect Transistor" (http://www.sciencemag.org/cgi/content/abstract/sci/302/5649/1380). *Science* **302** (6549): 1380–1382. doi: 10.1126/science.1091022 (http://dx.doi.org/10.1126/science.1091022). ISSN 1095-9203 (http://worldcat.org/issn/1095-9203). .

[19] http://www.nanohedron.com

[20] http://www.rnai.dk/

[21] http://www.cs.duke.edu/~thl/

[22] http://luolabs.bee.cornell.edu

[23] http://www.chem.purdue.edu/people/faculty/faculty.asp?itemID=46

[24] http://www.cs.duke.edu/~reif/BMC/Reif.BMCproject.html

[25] http://seemanlab4.chem.nyu.edu/

[26] http://research2.dfci.harvard.edu/shih/SHIH_LAB/Home.html

[27] http://www.physics.ox.ac.uk/cm/people/turberfield.htm

[28] http://dna.caltech.edu/

[29] http://chemistry.asu.edu/faculty/hao_yan.asp

[30] http://www.bell-labs.com/org/physicalsciences/profiles/yurke.html

[31] http://coen.boisestate.edu/departments/faculty.asp?ID=134

[32] http://www.biomolecular-modeling.com/Ascalaph/Ascalaph_Designer.html

[33] http://cadnano.org

[34] http://www.subirac.com

[35] http://www.nanoengineer-1.net

[36] http://www.isnsce.org/

Quantum evolution (alternative)

Quantum evolution is the hypothesis that genetic mutation can be adaptive, or directed through quantum effects.[1] It should not be confused with quantum evolution, a theory related to the modern evolutionary synthesis. The first publication on this subject, which appeared in a peer review journal, is by Vasily Ogryzko [2] . Biologist Johnjoe McFadden and the physicist Jim Al-Khalili subsequently published their own theory in 1999 [3] in which they proposed a mechanism based on enhanced decoherence of quantum states that interact strongly with the environment. McFadden published his book "Quantum Evolution" in 2000.[1]

Background

The "classical" Darwinian model of the evolution of cells is based on a mechanism whereby cells individually undergo mutation, with the process of natural selection then culling out those mutations which are less beneficial to the organism. **Quantum evolution** is an attempt to provide a theoretical mechanism which would skew these random mutations in favor of some outcome beneficial to the cell.

It should be stated at the outset that this theory would only be useful if indeed there were evidence that some sort of adaptive mutation occurs - in other words, if there were experimental data showing that the classical model of random mutation is lacking, and that certain mutations are "preferred" (occur more frequently) *because* they confer a greater benefit to the organism. This is in and of itself a controversial subject; as a plethora of papers have been published on the enigmatic phenomenon of adaptive mutation and the issue of their origin and mechanism remains unresolved. To date there is no such generally accepted explanation of the mechanism of adaptive mutation although most experimentalists would favour a process of random mutation accompanied by recombination and/or selection.

The mechanism proposed by quantum evolution is to imagine that the configuration of DNA in a cell is held in a quantum superposition of states, and that "mutations" occur as a result of a collapse of the superposition into the "best" configuration for the cell. The proponents of this approach liken the operation of DNA to the operation of a quantum computer, which selects one from a multitude of possible outcomes.

Several problems need to be overcome for this theory to be consistent with our current knowledge of quantum physics. Most importantly, the state of quantum superposition must last long enough to allow the DNA to do its normal job (produce RNA); otherwise, there would be no way for a comparison of the various outcomes of various mutations to occur, and thus no basis for the system to "decide" which mutations are more useful. Protein formation occurs at a rate of on the order of 10,000 times a second (10^{-5} seconds per protein formed). However, DNA is not translated directly into protein, instead DNA is transcribed into a messenger RNA and this RNA copy is then used for protein biosynthesis. A gene is therefore never directly linked to its protein product, making any possible mechanism for how a signal could be transmitted from a protein to the DNA that encodes it hard to imagine.

Although some have, by analogy to the technique of NMR imaging, posed state coherence times as long as half a second,[1] this analysis has been challenged[4] (but see also McFadden and Al-Khalili's rebuttal [5]) and coherence times on the order of 10^{-13} seconds seems to be a much more realistic outcome. This latter time would be far too short by many orders of magnitude for the protein formation required for a superposition of quantum states to affect mutations.

However recent evidence indicates that quantum coherence of electrons and protons does indeed occur in some (maybe all) enzyme reactions in living cells, such as those involved in photosynthesis [6] and may even be responsible for the huge catalytic enhancement of reaction rates provided by enzymes [7] .

If the theory of quantum evolution were indeed true, one could further speculate that a similar, more robust process could explain observed phenomena such as the apparent "jumps" in the fossil record as adaptive mutations on an even larger scale; this would require even longer periods of state coherence than those described by McFadden et al.[1] yet this has not been proposed by any of the advocates of quantum evolution who have limited their speculations to molecular processes.

A different critique on quantum evolution can be made by asking why, if the cell can make use of quantum superpositions, it's not used for more purposes? Our immune system contains "general" agents that attack anything foreign and "specialised" ones (antibodies) that bind to specific proteins on specific bacteria. The latter must be made on demand. But why not use quantum superpositions to immediately attack the bacteria with every conceivable antibody at the same time and select the one that works? The answer is likely to be that more complex systems (than single protons in DNA or electrons and protons in enzymes) cannot be maintained in quantum coherent states for long enough to have biological significance.

Science fiction writer Greg Egan, in his book *Teranesia*, posited a similar mechanism, whereby large adaptive mutations occur in multiple species under the aggressive quantum mechanical influence of a new protein.

Controversy

A primer on quantum mechanics (such as from David J. Griffiths' "Introduction to Quantum Mechanics") suggests that the very notion of having a molecule choose a state over all others purely based on what an exterior system, with no simultaneous effects on said molecule, is completely contrary to how quantum mechanics works. Quantum mechanical states are dependent on things like energy and other physical phenomena. Furthermore, imposing a viewpoint that one outcome is best implies that a best configuration needs some formal definition that is independent of mentioning organism lifespan, reproductivity, etc (as quantum mechanics does not depend on those things) and that the best configuration does depend on things such as energy levels, perturbations to the molecule, and similar things. When all of these are taken into consideration then the best state would seem to yield a truly random mutation as per what is perceived by humans as evolution.

However, the theory, at least that proposed by McFadden and Al-Khlaili [8] , did not propose that certain states are identified as 'best' by the quantum system but only that certain states interact with the environment more strongly than other states and thereby promote more rapid decoherence. For a starving cell, these more interactive states are those DNA states that encode mutations that allow the cell to grow.

Of course, DNA, like all molecules, already obeys the laws of quantum mechanics, including quantum superpositions, collapses, and tunneling. The consequences of these laws are more commonly known as quantum chemistry, which explains all of the familiar chemical laws. Since the chemical behavior of DNA is reasonably well-understood, and already includes both (ordinary) quantum mechanics and (ordinary) mutations, it is not yet clear where the additional effects of quantum evolution are supposed to arise.

See also

- Quantum mechanics
- Quantum mind
- Adaptive mutation

References

[1] McFadden, Johnjoe (2000). *Quantum Evolution*. (http://www.surrey.ac.uk/qe/quantumevolution.htm) HarperCollins. ISBN 0-00-255948-X; ISBN 0-00-655128-9

[2] Ogryzko, V. V. (1997). (http://fr.arxiv.org/abs/0704.0034) (http://fr.arxiv.org/abs/q-bio/0701050) (http://fr.arxiv.org/abs/0802.2271) (http://fr.arxiv.org/abs/0805.4316) *Biosystems* **43**, 83-95

[3] McFadden J. J. and Al-Khalili, J. V. (1999). A quantum mechanical model of adaptive mutation. (http://www.surrey.ac.uk/qe/pdfs/mcfadden_and_al-khalili.pdf?_ob=ArticleURL&_udi=B6T2K-3WHKRCP-4&_coverDate=06/30/1999&_alid=8659908&_rdoc=1&_fmt=summary&_orig=search&_qd=1&_cdi=4921&_sort=d&_acct=C000009958&_version=1&_urlVersion=0&_userid=121707&md5=7af163b1fd912ea4034c94d41561bc4f) (http://xyz.lanl.gov/abs/q-bio.OT/0701050) *Biosystems* **50**, 203-211

[4] Donald, Mathew J. (2001). *A Review of Quantum Evolution* (http://www.bss.phy.cam.ac.uk/~mjd1014/qevreva.html)

[5] (http://arxiv.org/abs/quant-ph/0110083v1) "Comment on Book Review of `Quantum Evolution' (Johnjoe McFadden) by Mathew J. Donald"

[6] (http://www.lbl.gov/Science-Articles/Archive/PBD-quantum-secrets.html) "Quantum sectrets of photosynthesis revealed"

[7] (http://www.pnas.org/cgi/content/full/105/4/1146) "Enzyme structure and dynamics affect hydrogen tunneling: The impact of a remote side chain (I553) in soybean lipoxygenase-1"

[8] Quantum Evolution: Outline page1 (http://www.surrey.ac.uk/qe/O1.htm)

Quantum evolution

For the alternative non-standard theory see: Quantum evolution (alternative).

Quantum evolution is a component of George Gaylord Simpson's multi-tempoed theory of evolutionary change, responsible for the rapid emergence of higher taxonomic groups. According to Simpson, evolutionary rates differ from group to group and even among closely related lineages. These different rates of evolutionary change were designated by Simpson as *horotelic* (medium tempo), *bradytelic* (slow tempo), and *tachytelic* (rapid tempo). Quantum evolution differed from these styles of change in that it involved a drastic shift in the adaptive zones of certain classes of animals. The word "quantum" therefore refers to an "all-or-none reaction," where transitional forms are particularly unstable, and perished rapidly and completely. Although quantum evolution may happen at any taxonomic level (1953, 389), it plays a much larger role in "the origin taxonomic units of relatively high rank, such as families, orders, and classes." (1944, 206)

According to Simpson (1944) quantum evolution relied heavily upon Sewall Wright's theory of random genetic drift. Simpson believed that major evolutionary transitions would arise when small populations—isolated and limited from gene flow—would fixate upon unusual gene combinations. This "inadaptive phase" (by genetic drift) would then (by natural selection) drive a deme population from one stable adaptive peak to another on the adaptive fitness landscape. However in his *Major Features of Evolution* (1953) Simpson wrote that it was still controversial "whether prospective adaptation as prelude to quantum evolution arises adaptively or inadaptively. It was concluded above that it usually arises adaptively . . . . The precise role of, say, genetic drift in this process thus is largely speculative at present. It may have an essential part or none. It surely is not involved in all cases of quantum evolution, but there is a strong possibility that it is often involved. If or when it is involved, it is an initiating mechanism. Drift can only rarely, and only for lower categories, have completed the transition to a new adaptive zone." (p. 390) This preference for adaptive over inadaptive forces lead Stephen Jay Gould to call attention to the "hardening of the Modern Synthesis" in the 1950s, where adaptationism took precedent over the pluralism of mechanisms common in the 1930s and 40s.

Simpson considered quantum evolution his crowning achievement, being "perhaps the most important outcome of [my] investigation, but also the most controversial and hypothetical." (1944, p. 206).

References

- Eldredge, Niles (1995). *Reinventing Darwin*. New York: John Wiley & Sons. pp. 20-26.
- Gould, S. J. (1980). "G. G. Simpson, Paleontology and the Modern Synthesis." [1] In E. Mayr and W. B. Provine, eds., *The Evolutionary Synthesis*. Cambridge MA: Harvard University Press, pp. 153-172.
- Gould, S. J. (1983). "The hardening of the Modern Synthesis" [2] In Marjorie Grene, ed., *Dimensions of Darwinism*. Cambridge UK: Cambridge University Press, pp. 71-93.
- Gould, S. J. (1994). "Tempo and mode in the macroevolutionary reconstruction on Darwinism" [3] *PNAS USA* **91**(15):6764-71.
- Gould S.J. (2002). *The Structure of Evolutionary Theory* Cambridge MA: Harvard Univ. Press. pp. 529-31. [4]
- Mayr, Ernst (1976). *Evolution and the Diversity of Life*. Cambridge MA: Belknap Press. p. 206. [5]
- Mayr, Ernst (1982). *The Growth of Biological Thought*. Cambridge MA: Belknap Press. pp. 555, 609-10. [6]
- Simpson, G. G. (1944). *Tempo and Mode in Evolution*. New York: Columbia Univ. Press.
- Simpson, G. G. (1953). *The Major Features of Evolution* [7]. New York: Columbia Univ. Press.

External links

- George Gaylord Simpson [8] - Biographical sketch.
- Tempo and Mode in Evolution: Genetics and Paleontology 50 Years After Simpson [9]

References

[1] http://books.google.com/books?id=NV5HcU9B2kQC&pg=PA153

[2] http://www.stephenjaygould.org/library/gould_synthesis.html

[3] http://www.pnas.org/cgi/reprint/91/15/6764.pdf

[4] http://books.google.com/books?id=nhIl7e61WOUC&pg=PP561

[5] http://books.google.com/books?id=uJS79Za7WZ0C&pg=PA206

[6] http://books.google.com/books?id=pHThtE2R0UQC&pg=PA609

[7] http://www.stephenjaygould.org/library/simpson_evolutionary-rates.html

[8] http://www.stephenjaygould.org/people/george_simpson.html

[9] http://darwin.nap.edu/books/0309051916/html

Molecular Dynamics and Biochemistry

Molecular dynamics

*Molecular dynamics (**MD**) is a form of computer simulation in which atoms and molecules are allowed to interact for a period of time by approximations of known physics,* giving a view of the motion of the particles. This kind of simulation is frequently used in the study of proteins and biomolecules, as well as in materials science. It is tempting, though not entirely accurate, to describe the technique as a "virtual microscope" with high temporal and spatial resolution. Whereas it is possible to take "still snapshots" of crystal structures and probe features of the motion of molecules through NMR, no experiment allows access to all the time scales of motion with atomic resolution. Richard Feynman once said that "If we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that all things are made of atoms, and that everything that living things do can be understood in terms of the jigglings and wigglings of atoms." Molecular dynamics lets scientists peer into the motion of individual atoms in a way which is not possible in laboratory experiments.

Molecular dynamics is a specialized discipline of molecular modeling and computer simulation based on statistical mechanics; the main justification of the MD method is that statistical ensemble averages are equal to time averages of the system, known as the ergodic hypothesis. MD has also been termed "statistical mechanics by numbers" and "Laplace's vision of Newtonian mechanics" of predicting the future by animating nature's forces[1] [2] and allowing insight into molecular motion on an atomic scale. However, long MD simulations are mathematically ill-conditioned, generating cumulative errors in numerical integration that can be minimized with proper selection of algorithms and parameters, but not eliminated entirely. Furthermore, current potential functions are, in many cases, not sufficiently accurate to reproduce the dynamics of molecular systems, so the much more computationally demanding Ab Initio Molecular Dynamics method must be used. Nevertheless, molecular dynamics techniques allow detailed time and space resolution into representative behavior in phase space for carefully selected systems.

Before it became possible to simulate molecular dynamics with computers, some undertook the hard work of trying it with physical models such as macroscopic spheres. The idea was to arrange them to replicate the properties of a liquid. J.D. Bernal said, in 1962: "... I took a number of rubber balls and stuck them together with rods of a selection of different lengths ranging from 2.75 to 4 inches. I tried to do this in the first place as casually as possible, working in my own office, being interrupted every five minutes or so and not remembering what I had done before the interruption."[3] Fortunately, now computers keep track of bonds during a simulation.

Because molecular systems generally consist of a vast number of particles, it is in general impossible to find the properties of such complex systems analytically. When the number of particles interacting is higher than two, the result is chaotic motion (see n-body problem). MD simulation circumvents the analytical intractability by using numerical methods. It represents an interface between laboratory experiments and theory, and can be understood as a "virtual experiment". MD probes the relationship between molecular structure, movement and function. Molecular dynamics is a multidisciplinary method. Its laws and theories stem from mathematics, physics, and chemistry, and it employs algorithms from computer science and information theory. It was originally conceived within theoretical physics in the late 1950s[4] and early 1960s [5], but is applied today mostly in materials science and the modeling of biomolecules.

Areas of Application

There is a significant difference between the focus and methods used by chemists and physicists, and this is reflected in differences in the jargon used by the different fields. In chemistry and biophysics, the interaction between the particles is either described by a "force field" (**classical MD**), a quantum chemical model, or a mix between the two. These terms are not used in physics, where the interactions are usually described by the name of the theory or approximation being used and called the potential energy, or just the "potential".

Give atoms initial positions $r^{(t=0)}$, choose short Δt

Get forces $\boldsymbol{F} = -\nabla V(\boldsymbol{r}^{(i)})$ and $\boldsymbol{a} = \boldsymbol{F}/m$

Move atoms: $\boldsymbol{r}^{(i+1)} = \boldsymbol{r}^{(i)} + \boldsymbol{v}^{(i)} \Delta t + \frac{1}{2} \boldsymbol{a} \Delta t^2 + \dots$

Move time forward: $t = t + \Delta t$

Repeat as long as you need

Highly simplified description of the molecular dynamics simulation algorithm. The simulation proceeds iteratively by alternatively calculating forces and solving the equations of motion based on the accelerations obtained from the new forces. In practise, almost all MD codes use much more complicated versions of the algorithm, including two steps (predictor and corrector) in solving the equations of motion and many additional steps for e.g. temperature and pressure control, analysis and output.

Beginning in theoretical physics, the method of MD gained popularity in materials science and since the 1970s also in biochemistry and biophysics. In chemistry, MD serves as an important tool in protein structure determination and refinement using experimental tools such as X-ray crystallography and NMR. It has also been applied with limited success as a method of refining protein structure predictions. In physics, MD is used to examine the dynamics of atomic-level phenomena that cannot be observed directly, such as thin film growth and ion-subplantation. It is also used to examine the physical properties of nanotechnological devices that have not or cannot yet be created.

In applied mathematics and theoretical physics, molecular dynamics is a part of the research realm of dynamical systems, ergodic theory and statistical mechanics in general. The concepts of energy conservation and molecular entropy come from thermodynamics. Some techniques to calculate conformational entropy such as principal components analysis come from information theory. Mathematical techniques such as the transfer operator become applicable when MD is seen as a Markov chain. Also, there is a large community of mathematicians working on volume preserving, symplectic integrators for more computationally efficient MD simulations.

MD can also be seen as a special case of the discrete element method (DEM) in which the particles have spherical shape (e.g. with the size of their van der Waals radii.) Some authors in the DEM community employ the term MD rather loosely, even when their simulations do not model actual molecules.

Design Constraints

Design of a molecular dynamics simulation should account for the available computational power. Simulation size (n=number of particles), timestep and total time duration must be selected so that the calculation can finish within a reasonable time period. However, the simulations should be long enough to be relevant to the time scales of the natural processes being studied. To make statistically valid conclusions from the simulations, the time span simulated should match the kinetics of the natural process. Otherwise, it is analogous to making conclusions about how a human walks from less than one footstep. Most scientific publications about the dynamics of proteins and DNA use data from simulations spanning nanoseconds (1E-9 s) to microseconds (1E-6 s). To obtain these simulations, several CPU-days to CPU-years are needed. Parallel algorithms allow the load to be distributed among CPUs; an example is the spatial or force decomposition decomposition [6].

During a classical MD simulation, the most CPU intensive task is the evaluation of the potential (force field) as a function of the particles' internal coordinates. Within that energy evaluation, the most expensive one is the

non-bonded or non-covalent part. In Big O notation, common molecular dynamics simulations scale by $O(n^2)$ if all pair-wise electrostatic and van der Waals interactions must be accounted for explicitly. This computational cost can be reduced by employing electrostatics methods such as Particle Mesh Ewald ($O(n\log(n))$), P3M or good spherical cutoff techniques ($O(n)$).

Another factor that impacts total CPU time required by a simulation is the size of the integration timestep. This is the time length between evaluations of the potential. The timestep must be chosen small enough to avoid discretization errors (i.e. smaller than the fastest vibrational frequency in the system). Typical timesteps for classical MD are in the order of 1 femtosecond (1E-15 s). This value may be extended by using algorithms such as SHAKE, which fix the vibrations of the fastest atoms (e.g. hydrogens) into place. Multiple time scale methods have also been developed, which allow for extended times between updates of slower long-range forces.[7] [8] [9]

For simulating molecules in a solvent, a choice should be made between explicit solvent and implicit solvent. Explicit solvent particles (such as the TIP3P, SPC/E and SPC-f water models) must be calculated expensively by the force field, while implicit solvents use a mean-field approach. Using an explicit solvent is computationally expensive, requiring inclusion of roughly ten times more particles in the simulation. But the granularity and viscosity of explicit solvent is essential to reproduce certain properties of the solute molecules. This is especially important to reproduce kinetics.

In all kinds of molecular dynamics simulations, the simulation box size must be large enough to avoid boundary condition artifacts. Boundary conditions are often treated by choosing fixed values at the edges (which may cause artifacts), or by employing periodic boundary conditions in which one side of the simulation loops back to the opposite side, mimicking a bulk phase.

Microcanonical ensemble (NVE)

In the **microcanonical**, or **NVE** ensemble, the system is isolated from changes in moles (N), volume (V) and energy (E). It corresponds to an adiabatic process with no heat exchange. A microcanonical molecular dynamics trajectory may be seen as an exchange of potential and kinetic energy, with total energy being conserved. For a system of N particles with coordinates X and velocities V, the following pair of first order differential equations may be written in Newton's notation as

$$F(X) = -\nabla U(X) = M\dot{V}(t)$$
$$V(t) = \dot{X}(t).$$

The potential energy function $U(X)$ of the system is a function of the particle coordinates X. It is referred to simply as the "potential" in Physics, or the "force field" in Chemistry. The first equation comes from Newton's laws; the force F acting on each particle in the system can be calculated as the negative gradient of $U(X)$.

For every timestep, each particle's position X and velocity V may be integrated with a symplectic method such as Verlet. The time evolution of X and V is called a trajectory. Given the initial positions (e.g. from theoretical knowledge) and velocities (e.g. randomized Gaussian), we can calculate all future (or past) positions and velocities.

One frequent source of confusion is the meaning of temperature in MD. Commonly we have experience with macroscopic temperatures, which involve a huge number of particles. But temperature is a statistical quantity. If there is a large enough number of atoms, statistical temperature can be estimated from the *instantaneous temperature*, which is found by equating the kinetic energy of the system to $nk_BT/2$ where n is the number of degrees of freedom of the system.

A temperature-related phenomenon arises due to the small number of atoms that are used in MD simulations. For example, consider simulating the growth of a copper film starting with a substrate containing 500 atoms and a deposition energy of 100 eV. In the real world, the 100 eV from the deposited atom would rapidly be transported through and shared among a large number of atoms (10^{10} or more) with no big change in temperature. When there are only 500 atoms, however, the substrate is almost immediately vaporized by the deposition. Something similar

happens in biophysical simulations. The temperature of the system in NVE is naturally raised when macromolecules such as proteins undergo exothermic conformational changes and binding.

Canonical ensemble (NVT)

In the canonical ensemble, moles (N), volume (V) and temperature (T) are conserved. It is also sometimes called constant temperature molecular dynamics (CTMD). In NVT, the energy of endothermic and exothermic processes is exchanged with a thermostat.

A variety of thermostat methods is available to add and remove energy from the boundaries of an MD system in a more or less realistic way, approximating the canonical ensemble. Popular techniques to control temperature include velocity rescaling, the Nosé-Hoover thermostat, Nosé-Hoover chains, the Berendsen thermostat and Langevin dynamics. Note that the Berendsen thermostat might introduce the flying ice cube effect, which leads to unphysical translations and rotations of the simulated system.

It is not trivial to obtain a canonical distribution of conformations and velocities using these algorithms. How this depends on system size, thermostat choice, thermostat parameters, time step and integrator is the subject of many articles in the field.

Isothermal-Isobaric (NPT) ensemble

In the isothermal-isobaric ensemble, moles (N), pressure (P) and temperature (T) are conserved. In addition to a thermostat, a barostat is needed. It corresponds most closely to laboratory conditions with a flask open to ambient temperature and pressure.

In the simulation of biological membranes, isotropic pressure control is not appropriate. For lipid bilayers, pressure control occurs under constant membrane area (NPAT) or constant surface tension "gamma" (NPγT).

Generalized ensembles

The replica exchange method is a generalized ensemble. It was originally created to deal with the slow dynamics of disordered spin systems. It is also called parallel tempering. The replica exchange MD (REMD) formulation [10] tries to overcome the multiple-minima problem by exchanging the temperature of non-interacting replicas of the system running at several temperatures.

Potentials in MD simulations

A molecular dynamics simulation requires the definition of a potential function, or a description of the terms by which the particles in the simulation will interact. In chemistry and biology this is usually referred to as a force field. Potentials may be defined at many levels of physical accuracy; those most commonly used in chemistry are based on molecular mechanics and embody a classical treatment of particle-particle interactions that can reproduce structural and conformational changes but usually cannot reproduce chemical reactions.

The reduction from a fully quantum description to a classical potential entails two main approximations. The first one is the Born-Oppenheimer approximation, which states that the dynamics of electrons is so fast that they can be considered to react instantaneously to the motion of their nuclei. As a consequence, they may be treated separately. The second one treats the nuclei, which are much heavier than electrons, as point particles that follow classical Newtonian dynamics. In classical molecular dynamics the effect of the electrons is approximated as a single potential energy surface, usually representing the ground state.

When finer levels of detail are required, potentials based on quantum mechanics are used; some techniques attempt to create hybrid classical/quantum potentials where the bulk of the system is treated classically but a small region is treated as a quantum system, usually undergoing a chemical transformation.

Empirical potentials

Empirical potentials used in chemistry are frequently called force fields, while those used in materials physics are called just empirical or analytical potentials.

Most force fields in chemistry are empirical and consist of a summation of bonded forces associated with chemical bonds, bond angles, and bond dihedrals, and non-bonded forces associated with van der Waals forces and electrostatic charge. Empirical potentials represent quantum-mechanical effects in a limited way through ad-hoc functional approximations. These potentials contain free parameters such as atomic charge, van der Waals parameters reflecting estimates of atomic radius, and equilibrium bond length, angle, and dihedral; these are obtained by fitting against detailed electronic calculations (quantum chemical simulations) or experimental physical properties such as elastic constants, lattice parameters and spectroscopic measurements.

Because of the non-local nature of non-bonded interactions, they involve at least weak interactions between all particles in the system. Its calculation is normally the bottleneck in the speed of MD simulations. To lower the computational cost, force fields employ numerical approximations such as shifted cutoff radii, reaction field algorithms, particle mesh Ewald summation, or the newer Particle-Particle Particle Mesh (P3M).

Chemistry force fields commonly employ preset bonding arrangements (an exception being *ab-initio* dynamics), and thus are unable to model the process of chemical bond breaking and reactions explicitly. On the other hand, many of the potentials used in physics, such as those based on the bond order formalism can describe several different coordinations of a system and bond breaking. Examples of such potentials include the Brenner potential[11] for hydrocarbons and its further developments for the C-Si-H and C-O-H systems. The ReaxFF potential[12] can be considered a fully reactive hybrid between bond order potentials and chemistry force fields.

Pair potentials vs. many-body potentials

The potential functions representing the non-bonded energy are formulated as a sum over interactions between the particles of the system. The simplest choice, employed in many popular force fields, is the "pair potential", in which the total potential energy can be calculated from the sum of energy contributions between pairs of atoms. An example of such a pair potential is the non-bonded Lennard-Jones potential (also known as the 6-12 potential), used for calculating van der Waals forces.

$$U(r) = 4\varepsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right]$$

Another example is the Born (ionic) model of the ionic lattice. The first term in the next equation is Coulomb's law for a pair of ions, the second term is the short-range repulsion explained by Pauli's exclusion principle and the final term is the dispersion interaction term. Usually, a simulation only includes the dipolar term, although sometimes the quadrupolar term is included as well.

$$U_{ij}(r_{ij}) = \sum \frac{z_i z_j}{4\pi\epsilon_0} \frac{1}{r_{ij}} + \sum A_l \exp \frac{-r_{ij}}{p_l} + \sum C_l r_{ij}^{-n_j} + \cdots$$

In many-body potentials, the potential energy includes the effects of three or more particles interacting with each other. In simulations with pairwise potentials, global interactions in the system also exist, but they occur only through pairwise terms. In many-body potentials, the potential energy cannot be found by a sum over pairs of atoms, as these interactions are calculated explicitly as a combination of higher-order terms. In the statistical view, the dependency between the variables cannot in general be expressed using only pairwise products of the degrees of freedom. For example, the Tersoff potential[13], which was originally used to simulate carbon, silicon and germanium and has since been used for a wide range of other materials, involves a sum over groups of three atoms, with the angles between the atoms being an important factor in the potential. Other examples are the embedded-atom method (EAM)[14] and the Tight-Binding Second Moment Approximation (TBSMA) potentials[15], where the electron density of states in the region of an atom is calculated from a sum of contributions from surrounding atoms,

and the potential energy contribution is then a function of this sum.

Semi-empirical potentials

Semi-empirical potentials make use of the matrix representation from quantum mechanics. However, the values of the matrix elements are found through empirical formulae that estimate the degree of overlap of specific atomic orbitals. The matrix is then diagonalized to determine the occupancy of the different atomic orbitals, and empirical formulae are used once again to determine the energy contributions of the orbitals.

There are a wide variety of semi-empirical potentials, known as tight-binding potentials, which vary according to the atoms being modeled.

Polarizable potentials

Most classical force fields implicitly include the effect of polarizability, e.g. by scaling up the partial charges obtained from quantum chemical calculations. These partial charges are stationary with respect to the mass of the atom. But molecular dynamics simulations can explicitly model polarizability with the introduction of induced dipoles through different methods, such as Drude particles or fluctuating charges. This allows for a dynamic redistribution of charge between atoms which responds to the local chemical environment.

For many years, polarizable MD simulations have been touted as the next generation. For homogenous liquids such as water, increased accuracy has been achieved through the inclusion of polarizability.[16] Some promising results have also been achieved for proteins.[17] However, it is still uncertain how to best approximate polarizability in a simulation.

Ab-initio methods

In classical molecular dynamics, a single potential energy surface (usually the ground state) is represented in the force field. This is a consequence of the Born-Oppenheimer approximation. If excited states, chemical reactions or a more accurate representation is needed, electronic behavior can be obtained from first principles by using a quantum mechanical method, such as Density Functional Theory. This is known as Ab Initio Molecular Dynamics (AIMD). Due to the cost of treating the electronic degrees of freedom, the computational cost of this simulations is much higher than classical molecular dynamics. This implies that AIMD is limited to smaller systems and shorter periods of time.

Ab-initio quantum-mechanical methods may be used to calculate the potential energy of a system on the fly, as needed for conformations in a trajectory. This calculation is usually made in the close neighborhood of the reaction coordinate. Although various approximations may be used, these are based on theoretical considerations, not on empirical fitting. *Ab-Initio* calculations produce a vast amount of information that is not available from empirical methods, such as density of electronic states or other electronic properties. A significant advantage of using *ab-initio* methods is the ability to study reactions that involve breaking or formation of covalent bonds, which correspond to multiple electronic states.

A popular software for *ab-initio* molecular dynamics is the Car-Parrinello Molecular Dynamics (CPMD) package based on the density functional theory.

Hybrid QM/MM

QM (quantum-mechanical) methods are very powerful. However, they are computationally expensive, while the MM (classical or molecular mechanics) methods are fast but suffer from several limitations (require extensive parameterization; energy estimates obtained are not very accurate; cannot be used to simulate reactions where covalent bonds are broken/formed; and are limited in their abilities for providing accurate details regarding the chemical environment). A new class of method has emerged that combines the good points of QM (accuracy) and

MM (speed) calculations. These methods are known as mixed or hybrid quantum-mechanical and molecular mechanics methods (hybrid QM/MM). The methodology for such techniques was introduced by Warshel and coworkers. In the recent years have been pioneered by several groups including: Arieh Warshel (University of Southern California), Weitao Yang (Duke University), Sharon Hammes-Schiffer (The Pennsylvania State University), Donald Truhlar and Jiali Gao (University of Minnesota) and Kenneth Merz (University of Florida).

The most important advantage of hybrid QM/MM methods is the speed. The cost of doing classical molecular dynamics (MM) in the most straightforward case scales $O(n^2)$, where N is the number of atoms in the system. This is mainly due to electrostatic interactions term (every particle interacts with every other particle). However, use of cutoff radius, periodic pair-list updates and more recently the variations of the particle-mesh Ewald's (PME) method has reduced this between $O(N)$ to $O(n^2)$. In other words, if a system with twice many atoms is simulated then it would take between twice to four times as much computing power. On the other hand the simplest *ab-initio* calculations typically scale $O(n^3)$ or worse (Restricted Hartree-Fock calculations have been suggested to scale $\sim O(n^{2.7})$). To overcome the limitation, a small part of the system is treated quantum-mechanically (typically active-site of an enzyme) and the remaining system is treated classically.

In more sophisticated implementations, QM/MM methods exist to treat both light nuclei susceptible to quantum effects (such as hydrogens) and electronic states. This allows generation of hydrogen wave-functions (similar to electronic wave-functions). This methodology has been useful in investigating phenomenon such as hydrogen tunneling. One example where QM/MM methods have provided new discoveries is the calculation of hydride transfer in the enzyme liver alcohol dehydrogenase. In this case, tunneling is important for the hydrogen, as it determines the reaction rate.[18]

Coarse-graining and reduced representations

At the other end of the detail scale are coarse-grained and lattice models. Instead of explicitly representing every atom of the system, one uses "pseudo-atoms" to represent groups of atoms. MD simulations on very large systems may require such large computer resources that they cannot easily be studied by traditional all-atom methods. Similarly, simulations of processes on long timescales (beyond about 1 microsecond) are prohibitively expensive, because they require so many timesteps. In these cases, one can sometimes tackle the problem by using reduced representations, which are also called coarse-grained models.

Examples for coarse graining (CG) methods are discontinuous molecular dynamics (CG-DMD)[19] [20] and Go-models[21] . Coarse-graining is done sometimes taking larger pseudo-atoms. Such united atom approximations have been used in MD simulations of biological membranes. The aliphatic tails of lipids are represented by a few pseudo-atoms by gathering 2-4 methylene groups into each pseudo-atom.

The parameterization of these very coarse-grained models must be done empirically, by matching the behavior of the model to appropriate experimental data or all-atom simulations. Ideally, these parameters should account for both enthalpic and entropic contributions to free energy in an implicit way. When coarse-graining is done at higher levels, the accuracy of the dynamic description may be less reliable. But very coarse-grained models have been used successfully to examine a wide range of questions in structural biology.

Examples of applications of coarse-graining in biophysics:

- protein folding studies are often carried out using a single (or a few) pseudo-atoms per amino acid;
- DNA supercoiling has been investigated using 1-3 pseudo-atoms per basepair, and at even lower resolution;
- Packaging of double-helical DNA into bacteriophage has been investigated with models where one pseudo-atom represents one turn (about 10 basepairs) of the double helix;
- RNA structure in the ribosome and other large systems has been modeled with one pseudo-atom per nucleotide.

The simplest form of coarse-graining is the "united atom" (sometimes called "extended atom") and was used in most early MD simulations of proteins, lipids and nucleic acids. For example, instead of treating all four atoms of a CH_3 methyl group explicitly (or all three atoms of CH_2 methylene group), one represents the whole group with a single

pseudo-atom. This pseudo-atom must, of course, be properly parameterized so that its van der Waals interactions with other groups have the proper distance-dependence. Similar considerations apply to the bonds, angles, and torsions in which the pseudo-atom participates. In this kind of united atom representation, one typically eliminates all explicit hydrogen atoms except those that have the capability to participate in hydrogen bonds ("polar hydrogens"). An example of this is the Charmm 19 force-field.

The polar hydrogens are usually retained in the model, because proper treatment of hydrogen bonds requires a reasonably accurate description of the directionality and the electrostatic interactions between the donor and acceptor groups. A hydroxyl group, for example, can be both a hydrogen bond donor and a hydrogen bond acceptor, and it would be impossible to treat this with a single OH pseudo-atom. Note that about half the atoms in a protein or nucleic acid are nonpolar hydrogens, so the use of united atoms can provide a substantial savings in computer time.

Examples of applications

Molecular dynamics is used in many fields of science.

- First macromolecular MD simulation published (1977, Size: 500 atoms, Simulation Time: 9.2 ps=0.0092 ns, Program: CHARMM precursor) Protein: Bovine Pancreatic Trypsine Inhibitor. This is one of the best studied proteins in terms of folding and kinetics. Its simulation published in Nature magazine paved the way for understanding protein motion as essential in function and not just accessory.[22]

- MD is the standard method to treat collision cascades in the heat spike regime, i.e. the effects that energetic neutron and ion irradiation have on solids an solid surfaces.[23] [24]

The following two biophysical examples are not run-of-the-mill MD simulations. They illustrate almost heroic efforts to produce simulations of a system of very large size (a complete virus) and very long simulation times (500 microseconds):

- MD simulation of the complete satellite tobacco mosaic virus (**STMV**) (2006, Size: 1 million atoms, Simulation time: 50 ns, program: NAMD) This virus is a small, icosahedral plant virus which worsens the symptoms of infection by Tobacco Mosaic Virus (TMV). Molecular dynamics simulations were used to probe the mechanisms of viral assembly. The entire STMV particle consists of 60 identical copies of a single protein that make up the viral capsid (coating), and a 1063 nucleotide single stranded RNA genome. One key finding is that the capsid is very unstable when there is no RNA inside. The simulation would take a single 2006 desktop computer around 35 years to complete. It was thus done in many processors in parallel with continuous communication between them.[25]

- Folding Simulations of the Villin Headpiece in All-Atom Detail (2006, Size: 20,000 atoms; Simulation time: 500 µs = 500,000 ns, Program: folding@home) This simulation was run in 200,000 CPU's of participating personal computers around the world. These computers had the folding@home program installed, a large-scale distributed computing effort coordinated by Vijay Pande at Stanford University. The kinetic properties of the Villin Headpiece protein were probed by using many independent, short trajectories run by CPU's without continuous real-time communication. One technique employed was the Pfold value analysis, which measures the probability of folding before unfolding of a specific starting conformation. Pfold gives information about transition state structures and an ordering of conformations along the folding pathway. Each trajectory in a Pfold calculation can be relatively short, but many independent trajectories are needed.[26]

Molecular dynamics algorithms

Integrators

- Verlet-Stoermer integration
- Runge-Kutta integration
- Beeman's algorithm
- Gear predictor - corrector
- Constraint algorithms (for constrained systems)
- Symplectic integrator

Short-range interaction algorithms

- Cell lists
- Verlet list
- Bonded interactions

Long-range interaction algorithms

- Ewald summation
- Particle Mesh Ewald (PME)
- Particle-Particle Particle Mesh P3M
- Reaction Field Method

Parallelization strategies

- Domain decomposition method (Distribution of system data for parallel computing)
- Molecular Dynamics - Parallel Algorithms [27]

Major software for MD simulations

- Abalone (classical, implicit water)
- ABINIT (DFT)
- ACEMD [28] (running on NVIDIA GPUs: heavily optimized with CUDA)
- ADUN [29] (classical, P2P database for simulations)
- AMBER (classical)
- Ascalaph [30] (classical, GPU accelerated)
- CASTEP (DFT)
- CPMD (DFT)
- CP2K [31] (DFT)
- CHARMM (classical, the pioneer in MD simulation, extensive analysis tools)
- COSMOS [32] (classical and hybrid QM/MM, quantum-mechanical atomic charges with BPT)
- Desmond (classical, parallelization with up to thousands of CPU's)
- Culgi [33] (classical, OPLS-AA, Dreiding, Nerd, and TraPPE-UA force fields)
- DL_POLY [34] (classical)
- ESPResSo (classical, coarse-grained, parallel, extensible)
- Fireball [35] (tight-binding DFT)
- GROMACS (classical)
- GROMOS (classical)
- GULP (classical)
- Hippo [36] (classical)

- Kalypso [37] MD simulation of atomic collisions in solids
- LAMMPS (classical, large-scale with spatial-decomposition of simulation domain for parallelism)
- LPMD [38] Las Palmeras Molecular Dynamics: flexible an modular MD.
- MacroModel (classical)
- MDynaMix (classical, parallel)
- MOLDY [39] (classical, parallel) latest release [40]
- Materials Studio [41] (Forcite MD using COMPASS, Dreiding, Universal, cvff and pcff forcefields in serial or parallel, QMERA (QM+MD), ONESTEP (DFT), etc.)
- MOSCITO (classical)
- NAMD (classical, parallelization with up to thousands of CPU's)
- NEWTON-X [42] (ab initio, surface-hopping dynamics)
- ORAC (classical)
- ProtoMol [43] (classical, extensible, includes multigrid electrostatics)
- PWscf (DFT)
- RedMD [44] (coarse-grained simulations package on GNU licence)
- S/PHI/nX [45] (DFT)
- SIESTA (DFT)
- VASP (DFT)
- TINKER (classical)
- YASARA [46] (classical)
- XMD (classical)

Related software

- VMD - MD simulation trajectories can be visualized and analyzed.
- PyMol - Molecular Visualization software written in python
- Packmol [47] Package for building starting configurations for MD in an automated fashion
- Sirius - Molecular modeling, analysis and visualization of MD trajectories
- esra [48] - Lightweight molecular modeling and analysis library (Java/Jython/Mathematica).
- Molecular Workbench [49] - Interactive molecular dynamics simulations on your desktop
- BOSS - MC in OPLS

Specialized hardware for MD simulations

- Anton - A specialized, massively parallel supercomputer designed to execute MD simulations.
- MDGRAPE - A special purpose system built for molecular dynamics simulations, especially protein structure prediction.

See also

- Molecular graphics
- Molecular modeling
- Computational chemistry
- Energy drift
- Force field (chemistry)
- Force field implementation
- Monte Carlo method
- Molecular design software
- Molecular mechanics

- Molecular modeling on GPU
- Protein dynamics
- Implicit solvation
- Car-Parrinello method
- Symplectic numerical integration
- Software for molecular mechanics modeling
- Dynamical systems
- Theoretical chemistry
- Statistical mechanics
- Quantum chemistry
- Discrete element method
- List of nucleic acid simulation software

References

[1] Schlick, T. (1996). "Pursuing Laplace's Vision on Modern Computers". in J. P. Mesirov, K. Schulten and D. W. Sumners. *Mathematical Applications to Biomolecular Structure and Dynamics, IMA Volumes in Mathematics and Its Applications*. **82**. New York: Springer-Verlag. pp. 218−247. ISBN 978-0387948386.

[2] de Laplace, P. S. (1820) (in French). *Oeuveres Completes de Laplace, Theorie Analytique des Probabilites*. Paris, France: Gauthier-Villars.

[3] Bernal, J.D. (1964). "The Bakerian lecture, 1962: The structure of liquids". *Proc. R. Soc.* **280**: 299−322. doi: 10.1098/rspa.1964.0147 (http://dx.doi.org/10.1098/rspa.1964.0147).

[4] Alder, B. J.; T. E. Wainwright (1959). "Studies in Molecular Dynamics. I. General Method". *J. Chem. Phys.* **31** (2): 459. doi: 10.1063/1.1730376 (http://dx.doi.org/10.1063/1.1730376).

[5] A. Rahman (1964). "Correlations in the Motion of Atoms in Liquid Argon". *Phys Rev* **136**: A405-A411. doi: 10.1103/PhysRev.136.A405 (http://dx.doi.org/10.1103/PhysRev.136.A405).

[6] http://www.sandia.gov/~sjplimp/md.html

[7] Streett WB, Tildesley DJ, Saville G (1978). "Multiple time-step methods in molecular dynamics". *Mol Phys* **35** (3): 639−648. doi: 10.1080/00268977800100471 (http://dx.doi.org/10.1080/00268977800100471).

[8] Tuckerman ME, Berne BJ, Martyna GJ (1991). "Molecular dynamics algorithm for multiple time scales: systems with long range forces". *J Chem Phys* **94** (10): 6811−6815.

[9] Tuckerman ME, Berne BJ, Martyna GJ (1992). "Reversible multiple time scale molecular dynamics". *J Chem Phys* **97** (3): 1990−2001. doi: 10.1063/1.463137 (http://dx.doi.org/10.1063/1.463137).

[10] Sugita, Yuji; Yuko Okamoto (1999). "Replica-exchange molecular dynamics method for protein folding". *Chem Phys Letters* **314**: 141−151. doi: 10.1016/S0009-2614(99)01123-9 (http://dx.doi.org/10.1016/S0009-2614(99)01123-9).

[11] Brenner, D. W. (1990). "Empirical potential for hydrocarbons for use in simulating the chemical vapor deposition of diamond films". *Phys. Rev. B* **42** (15): 9458. doi: 10.1103/PhysRevB.42.9458 (http://dx.doi.org/10.1103/PhysRevB.42.9458).

[12] van Duin, A.; Siddharth Dasgupta, Francois Lorant and William A. Goddard III (2001). *J. Phys. Chem. A* **105**: 9398.

[13] Tersoff, J. (1989). ""Modeling solid-state chemistry: Interatomic potentials for multicomponent systems". *Phys. Rev. B* **39**: 5566. doi: 10.1103/PhysRevB.39.5566 (http://dx.doi.org/10.1103/PhysRevB.39.5566).

[14] Daw, M. S.; S. M. Foiles and M. I. Baskes (1993). "The embedded-atom method: a review of theory and applications". *Mat. Sci. And Engr. Rep.* **9**: 251. doi: 10.1016/0920-2307(93)90001-U (http://dx.doi.org/10.1016/0920-2307(93)90001-U).

[15] Cleri, F.; V. Rosato (1993). "Tight-binding potentials for transition metals and alloys". *Phys. Rev. B* **48**: 22. doi: 10.1103/PhysRevB.48.22 (http://dx.doi.org/10.1103/PhysRevB.48.22).

[16] Lamoureux G, Harder E, Vorobyov IV, Roux B, MacKerell AD (2006). "A polarizable model of water for molecular dynamics simulations of biomolecules". *Chem Phys Lett* **418**: 245−249. doi: 10.1016/j.cplett.2005.10.135 (http://dx.doi.org/10.1016/j.cplett.2005.10.135).

[17] Patel, S.; MacKerell, Jr. AD; Brooks III, Charles L (2004). "CHARMM fluctuating charge force field for proteins: II protein/solvent properties from molecular dynamics simulations using a nonadditive electrostatic model". *J Comput Chem* **25**: 1504−1514. doi: 10.1002/jcc.20077 (http://dx.doi.org/10.1002/jcc.20077).

[18] Billeter, SR; SP Webb, PK Agarwal, T Iordanov, S Hammes-Schiffer (2001). "Hydride Transfer in Liver Alcohol Dehydrogenase: Quantum Dynamics, Kinetic Isotope Effects, and Role of Enzyme Motion". *J Am Chem Soc* **123**: 11262−11272. doi: 10.1021/ja011384b (http://dx.doi.org/10.1021/ja011384b).

[19] Smith, A; CK Hall (2001). "Alpha-Helix Formation: Discontinuous Molecular Dynamics on an Intermediate-Resolution Protein Model". *Proteins* **44**: 344−360.

[20] Ding, F; JM Borreguero, SV Buldyrey, HE Stanley, NV Dokholyan (2003). "Mechanism for the alpha-helix to beta-hairpin transition". *J Am Chem Soc* **53**: 220−228. doi: 10.1002/prot.10468 (http://dx.doi.org/10.1002/prot.10468).

[21] Paci, E; M Vendruscolo, M Karplus (2002). "Validity of Go Models: Comparison with a Solvent-Shielded Empirical Energy Decomposition". *Biophys J* **83**: 3032–3038. doi: 10.1016/S0006-3495(02)75308-3 (http://dx.doi.org/10.1016/S0006-3495(02)75308-3).

[22] McCammon, J; JB Gelin, M Karplus (1977). "Dynamics of folded proteins". *Nature* **267**: 585–590. doi: 10.1038/267585a0 (http://dx.doi.org/10.1038/267585a0).

[23] Averback, R. S.; Diaz de la Rubia, T. (1998). "Displacement damage in irradiated metals and semiconductors". in H. Ehrenfest and F. Spaepen. *Solid State Physics*. **51**. New York: Academic Press. p. 281–402.

[24] R. Smith, ed (1997). *Atomic & ion collisions in solids and at surfaces: theory, simulation and applications*. Cambridge, UK: Cambridge University Press.

[25] Freddolino P, Arkhipov A, Larson SB, McPherson A, Schulten K. "Molecular dynamics simulation of the Satellite Tobacco Mosaic Virus (STMV)" (http://www.ks.uiuc.edu/Research/STMV/). *Theoretical and Computational Biophysics Group*. University of Illinois at Urbana Champaign. .

[26] The Folding@Home Project (http://folding.stanford.edu/) and recent papers (http://folding.stanford.edu/papers.html) published using trajectories from it. Vijay Pande Group. Stanford University

[27] http://www.cs.sandia.gov/~sjplimp/md.html

[28] http://www.acellera.com/index.php?arg=acemd

[29] http://cbbl.imim.es/Adun

[30] http://www.biomolecular-modeling.com/Products.html

[31] http://cp2k.berlios.de/

[32] http://www.cosmos-software.de/ce_intro.html

[33] http://www.culgi.com/

[34] http://www.ccp5.ac.uk/DL_POLY/

[35] http://fireball-dft.org

[36] http://www.biowerkzeug.com/

[37] http://sites.google.com/site/KalypsoSimulation/

[38] http://www.gnm.cl/lpmd

[39] http://www.ccp5.ac.uk/moldy/moldy.html

[40] http://ccpforge.cse.rl.ac.uk/frs/?group_id=34

[41] http://accelrys.com/products/materials-studio/

[42] http://www.univie.ac.at/newtonx/

[43] http://protomol.sourceforge.net/

[44] http://bionano.icm.edu.pl/software/redmd

[45] http://www.sphinxlib.de

[46] http://www.yasara.org

[47] http://www.ime.unicamp.br/~martinez/packmol

[48] http://esra.sourceforge.net/cgi-bin/index.cgi

[49] http://mw.concord.org/modeler/

General references

- M. P. Allen, D. J. Tildesley (1989) Computer simulation of liquids. Oxford University Press. ISBN 0-19-855645-4.

- J. A. McCammon, S. C. Harvey (1987) Dynamics of Proteins and Nucleic Acids. Cambridge University Press. ISBN 0521307503 (hardback).

- D. C. Rapaport (1996) The Art of Molecular Dynamics Simulation. ISBN 0-521-44561-2.

- Frenkel, Daan; Smit, Berend (2002) [2001]. *Understanding Molecular Simulation : from algorithms to applications*. San Diego, California: Academic Press. ISBN 0-12-267351-4.

- J. M. Haile (2001) Molecular Dynamics Simulation: Elementary Methods. ISBN 0-471-18439-X

- R. J. Sadus, *Molecular Simulation of Fluids: Theory, Algorithms and Object-Orientation*, 2002, ISBN 0-444-51082-6

- Oren M. Becker, Alexander D. Mackerell Jr, Benoît Roux, Masakatsu Watanabe (2001) Computational Biochemistry and Biophysics. Marcel Dekker. ISBN 0-8247-0455-X.

- Andrew Leach (2001) Molecular Modelling: Principles and Applications. (2nd Edition) Prentice Hall. ISBN 978-0582382107.

- Tamar Schlick (2002) Molecular Modeling and Simulation. Springer. ISBN 0-387-95404-X.

- William Graham Hoover (1991) Computational Statistical Mechanics, Elsevier, ISBN 0-444-88192-1.

- D.J. Evans and G.P. Morriss (2008) Statistical Mechanics of Nonequilibrium Liquids, Second Edition, Cambridge University Press,ISBN 978-0-521-85791-8.

External links

- The Blue Gene Project (http://researchweb.watson.ibm.com/bluegene/) (IBM)JawBreakers.org
- D. E. Shaw Research (http://deshawresearch.com/) (D. E. Shaw Research)
- Molecular Physics (http://www.tandf.co.uk/journals/titles/00268976.asp)
- Statistical mechanics of Nonequilibrium Liquids (http://www.phys.unsw.edu.au/~gary/book.html) Lecture Notes on non-equilibrium MD
- Introductory Lecture on Classical Molecular Dynamics (http://www.fz-juelich.de/nic-series/volume10/sutmann.pdf) by Dr. Godehard Sutmann, NIC, Forschungszentrum Jülich, Germany
- Introductory Lecture on Ab Initio Molecular Dynamics and Ab Initio Path Integrals (http://www.fz-juelich.de/nic-series/volume10/tuckerman2.pdf) by Mark E. Tuckerman, New York University, USA
- Introductory Lecture on Ab initio molecular dynamics: Theory and Implementation (http://www.fz-juelich.de/nic-series/Volume1/marx.pdf) by Dominik Marx, Ruhr-Universität Bochum and Jürg Hutter, Universität Zürich

Force field (chemistry)

In the context of molecular mechanics, a **force field** (also called a **forcefield**) refers to the functional form and parameter sets used to describe the potential energy of a system of particles (typically but not necessarily atoms). Force field functions and parameter sets are derived from both experimental work and high-level quantum mechanical calculations. "All-atom" force fields provide parameters for every atom in a system, including hydrogen, while "united-atom" force fields treat the hydrogen and carbon atoms in methyl and methylene groups as a single interaction center. "Coarse-grained" force fields, which are frequently used in long-time simulations of proteins, provide even more abstracted representations for increased computational efficiency.

The usage of the term "force field" in chemistry and computational biology differs from the standard usage in physics. In chemistry usage a force field is defined as a potential function, while the term is used in physics to denote the negative gradient of a scalar potential.
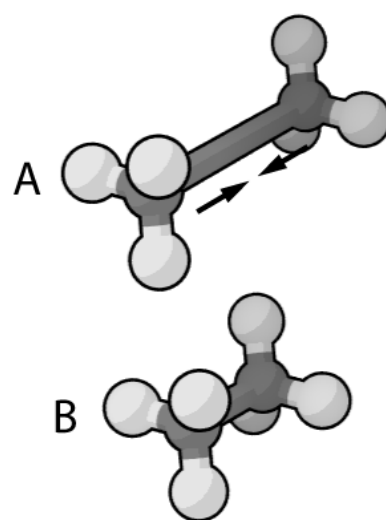
A force field is used to minimize the bond stretching energy of this ethane molecule.

Functional form

Molecular mechanics potential energy function
with continuum solvent.
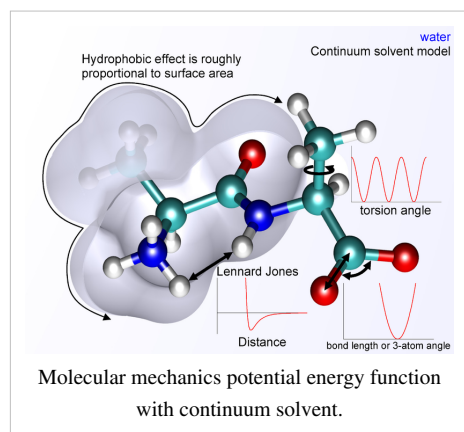
The basic functional form of a force field encapsulates both bonded terms relating to atoms that are linked by covalent bonds, and nonbonded (also called "noncovalent") terms describing the long-range electrostatic and van der Waals forces. The specific decomposition of the terms depends on the force field, but a general form for the total energy in an additive force field can be written as $E_{total} = E_{bonded} + E_{nonbonded}$ where the components of the covalent and noncovalent contributions are given by the following summations:

$$E_{bonded} = E_{bond} + E_{angle} + E_{dihedral}$$
$$E_{nonbonded} = E_{electrostatic} + E_{vanderWaals}$$

The bond and angle terms are usually modeled as harmonic oscillators in force fields that do not allow bond breaking. A more realistic description of a covalent bond at higher stretching is provided by the more expensive Morse potential. The functional form for the rest of the bonded terms is highly variable. Proper dihedral potentials are usually included. Additionally, "improper torsional" terms may be added to enforce the planarity of aromatic rings and other conjugated systems, and "cross-terms" that describe coupling of different internal variables, such as angles and bond lengths. Some force fields also include explicit terms for hydrogen bonds.

The nonbonded terms are most computationally intensive because they include many more interactions per atom. A popular choice is to limit interactions to pairwise energies. The van der Waals term is usually computed with a Lennard-Jones potential and the electrostatic term with Coulomb's law, although both can be buffered or scaled by a constant factor to account for electronic polarizability and produce better agreement with experimental observations.

Parameterization

In addition to the functional form of the potentials, a force field defines a set of parameters for each type of atom. For example, a force field would include distinct parameters for an oxygen atom in a carbonyl functional group and in a hydroxyl group. The typical parameter set includes values for atomic mass, van der Waals radius, and partial charge for individual atoms, and equilibrium values of bond lengths, bond angles, and dihedral angles for pairs, triplets, and quandruplets of bonded atoms, and values corresponding to the effective spring constant for each potential. Most current force fields use a "fixed-charge" model by which each atom is assigned a single value for the atomic charge that is not affected by the local electrostatic environment; proposed developments in next-generation force fields incorporate models for polarizability, in which a particle's charge is influenced by electrostatic interactions with its neighbors. For example, polarizability can be approximated by the introduction of induced dipoles; it can also be represented by Drude particles, or massless, charge-carrying virtual sites attached by a springlike harmonic potential to each polarizable atom. The introduction of polarizability into force fields in common use has been inhibited by the high computational expense associated with calculating the local electrostatic field.

Although many molecular simulations involve biological macromolecules such as proteins, DNA, and RNA, the parameters for given atom types are generally derived from observations on small organic molecules that are more tractable for experimental studies and quantum calculations. Different force fields can be derived from dissimilar types of experimental data, such as enthalpy of vaporization (OPLS), enthalpy of sublimation (CFF), dipole moments, or various spectroscopic parameters (CFF).

Parameter sets and functional forms are defined by force field developers to be self-consistent. Because the functional forms of the potential terms vary extensively between even closely related force fields (or successive versions of the same force field), the parameters from one force field should never be used in conjunction with the potential from another.

Deficiencies

All force fields are based on numerous approximations and derived from different types of experimental data. Therefore they are called *empirical*. Some existing force fields usually do not account for electronic polarization of the environment, an effect that can significantly reduce electrostatic interactions of partial atomic charges. This problem was addressed by developing "polarizable force fields" [1] [2] or using macroscopic dielectric constant. However, application of a single value of dielectric constant is questionable in the highly heterogeneous environments of proteins or biological membranes, and the nature of the dielectric depends on the model used [3].

All types of van der Waals forces are also strongly environment-dependent, because these forces originate from interactions of induced and "instantaneous" dipoles (see Intermolecular force). The original Fritz London theory of these forces can only be applied in vacuum. A more general theory of van der Waals forces in condensed media was developed by A. D. McLachlan in 1963 (this theory includes the original London's approach as a special case) [4]. The McLachlan theory predicts that van der Waals attractions in media are weaker than in vacuum and follow the "like dissolves like" rule, which means that different types of atoms interact more weakly than identical types of atoms. [5]. This is in contrast to "combinatorial rules" or Slater-Kirkwood equation applied for development of the classical force fields. The "combinatorial rules" state that interaction energy of two dissimilar atoms (e.g. C…N) is an average of the interaction energies of corresponding identical atom pairs (i.e. C…C and N…N). According to McLachlan theory, the interactions of particles in a media can even be completely repulsive, as observed for liquid helium [4]. The conclusions of McLachlan theory are supported by direct measurements of attraction forces between different materials (Hamaker constant), as explained by Jacob Israelachvili in his book "Intermolecular and surface forces". It was concluded that "*the interaction between hydrocarbons across water is about 10% of that across vacuum*" [4]. Such effects are unaccounted in the standard molecular mechanics.

Another round of criticism came from practical applications, such as protein structure refinement. It was noted that CASP participants did not try to refine their models to avoid "*a central embarrassment of molecular mechanics, namely that energy minimization or molecular dynamics generally leads to a model that is less like the experimental structure*". [6] Actually, the force fields have been successfully applied for protein structure refinement in different X-ray crystallography and NMR spectroscopy applications, especially using program XPLOR [7]. However, such refinement is driven primarily by a set of experimental constraints, whereas the force fields serve merely to remove interatomic hindrances. The results of calculations are practically the same with rigid sphere potentials implemented in program DYANA [8] (calculations from NMR data), or with programs for crystallographic refinement that do not use any energy functions. The deficiencies of the force fields remain a major bottleneck in homology modeling of proteins [9]. Such situation gave rise to development of alternative empirical scoring functions specifically for ligand docking [10], protein folding [11] [12] [13], computational protein design [14] [15] [16], and modeling of proteins in membranes [17].

There is also an opinion that molecular mechanics may operate with energy which is irrelevant to protein folding or ligand binding [18]. The parameters of typical force fields reproduce enthalpy of sublimation, i.e. energy of evaporation of molecular crystals. However, it was recognized that protein folding and ligand binding are

thermodynamically very similar to crystallization, or liquid-solid transitions, because all these processes represent "freezing" of mobile molecules in condensed media [19] [20] [21] . Therefore, free energy changes during protein folding or ligand binding are expected to represent a combination of an energy similar to heat of fusion (energy absorbed during melting of molecular crystals), a conformational entropy contribution, and solvation free energy. The heat of fusion is significantly smaller than enthalpy of sublimation [4] . Hence, the potentials describing protein folding or ligand binding must be weaker than potentials in molecular mechanics. Indeed, the energies of H-bonds in proteins are ~ -1.5 kcal/mol when estimated from protein engineering or alpha helix to coil transition data [22] [23] , but the same energies estimated from sublimation enthalpy of molecular crystals were -4 to -6 kcal/mol [24] . The depths of modified Lennard-Jones potentials derived from protein engineering data were also smaller than in typical force fields and followed the "like dissolves like" rule, as predicted by McLachlan theory [18] .

Popular force fields

Different force fields are designed for different purposes.

MM2 was developed by Norman Allinger primarily for conformational analysis of hydrocarbons and other small organic molecules. It is designed to reproduce the equilibrium covalent geometry of molecules as precisely as possible. It implements a large set of parameters that is continuously refined and updated for many different classes of organic compounds (MM3 and MM4).[25] [26] [27] [28] [29]

CFF was developed by Warshel, Lifson and coworkers as a general method for unifying studies of energies, structures and vibration of general molecules and molecular crystals. The CFF program, developed by Levitt and Warshel, is based on the Cartesian representation of all the atoms, and it served as the basis for many subsequent simulation programs.

ECEPP was developed specifically for modeling of peptides and proteins. It uses fixed geometries of amino acid residues to simplify the potential energy surface. Thus, the energy minimization is conducted in the space of protein torsion angles. Both MM2 and ECEPP include potentials for H-bonds and torsion potentials for describing rotations around single bonds. ECEPP/3 was implemented (with some modifications) in Internal Coordinate Mechanics and FANTOM [30] .

AMBER, CHARMM and GROMOS have been developed primarily for molecular dynamics of macromolecules, although they are also commonly applied for energy minimization. Therefore, the coordinates of all atoms are considered as free variables.

Classical force fields

- AMBER (Assisted Model Building and Energy Refinement)] - widely used for proteins and DNA
- CHARMM (Chemistry at HARvard Molecular Mechanics)] - originally developed at Harvard, widely used for both small molecules and macromolecules
- CHARMm - commercial version of CHARMM, available through Accelrys
- CVFF - also broadly used for small molecules and macromolecules
- COSMOS-NMR - hybrid QM/MM forcefield adapted to a variety of inorganic compounds, organic compounds and biological macromolecules, including semi-empirical calculation of atomic charges and NMR properties. COSMOS-NMR is optimized for NMR based structure elucidation and implemented in COSMOS molecular modelling package.[31]
- GROMACS - The force field optimized for the package of the same name
- GROMOS - A force field that comes as part of the GROMOS [32] (GROningen MOlecular Simulation package), a general-purpose molecular dynamics computer simulation package for the study of biomolecular systems. GROMOS force field (A-version) has been developed for application to aqueous or apolar solutions of proteins, nucleotides and sugars. However, a gas phase version (B-version) for simulation of isolated molecules is also available

- OPLS (Optimized Potential for Liquid Simulations) (variations include OPLS-AA, OPLS-UA, OPLS-2001, OPLS-2005) developed by William L. Jorgensen [33] at the Yale University Department of Chemistry.
- ENZYMIX [34] – A general polarizable force field for modeling chemical reactions in biological molecules. This force field is implemented with the empirical valence bond (EVB) method and is also combined with the semimacroscopic PDLD approach in the program in the MOLARIS [35] package.
- ECEPP/2 [36] - First force field for polypeptide molecules - developed by F.A.Momany, H.A.Scheraga and colleagues.
- QCFF/PI – A general force field for conjugated molecules. [37] . [38]

Second-generation force fields

- CFF - a family of forcefields adapted to a broad variety of organic compounds, includes force fields for polymers, metals, etc.
- MMFF (Merck Molecular Force Field)- developed at Merck, for a broad range of molecules
- MM2, MM3, MM4 - developed by Norman Allinger, parametrized for a broad range of molecules
- QVBMM [39] - developed by Vernon G. S. Box, parameterized for all biomolecules and a broad range of organic molecules, and implemented in STR3DI32

Polarizable force field based on induced dipole

- CFF/ind and ENZYMIX – The first polarizable force field [40] which has subsequently been used in many applications to biological systems.[2] .
- DRF90 [41] developed by P. Th. van Duijnen and coworkers.

Polarizable Force Fields based on point charges

- PFF (Polarizable Force Field) developed by Richard A. Friesner and coworkers
- SP-basis Chemical Potential Equalization (CPE) approach developed by R. Chelli and P. Procacci
- CHARMM polarizable force field developed by S. Patel (University of Delaware) and C. L. Brooks III (University of Michigan).
- AMBER polarizable force field developed by Jim Caldwell and coworkers.

Polarizable Force Fields based on distributed multipoles

- The SIBFA (Sum of Interactions Between Fragments Ab initio computed) [42] force field [43] for small molecules and flexible proteins, developed by Nohad Gresh (Paris V, René Descartes University) and Jean-Philip Piquemal (Paris VI, Pierre & Marie Curie University). SIBFA is a molecular mechanics procedure formulated and calibrated on the basis of ab initio supermolecule computations. Its purpose is to enable the simultaneous and reliable computations of both intermolecular and conformational energies governing the binding specificities of biologically and pharmacologically relevant molecules. This procedure enables an accurate treatment of transition metals. The inclusion of a ligand field contribution allows computations on "open-shell" metalloproteins.
- AMOEBA (Atomic Multipole Optimized Energetics for Biomolecular Applications) [44] force field developed by Pengyu Ren (University of Texas at Austin) and Jay W. Ponder (Washington University).
- ORIENT procedure [45] developed by Anthony J. Stone (Cambridge University) and coworkers.
- Non-Empirical Molecular Orbital (NEMO) procedure developed by Gunnar Karlström and coworkers at Lund University (Sweden).

Polarizable Force Fields based on density

- - Gaussian Electrostatic Model (GEM)[43] [46] [47] , a polarizable force field based on Density Fitting developed by Thomas A. Darden and G. Andrés Cisneros at NIEHS; and Jean-Philip Piquemal (Paris VI University).
- - Polarizable procedure based on the Kim-Gordon approach developed by Jürg Hutter and coworkers (University of Zurick)

Polarizable Force Fields based on Bond Polarization Theory (BPT)

- COSMOS-NMR (Computer Simulation of Molecular Structure) developed by Ulrich Sternberg and coworkers. Hybrid QM/MM force field enables explicit quantum-mechanical calculation of electrostatic properties using localized bond orbitals with fast BPT formalism.[48] Atomic charge fluctuation is possible in each molecular dynamics step.

Reactive Force Fields

- ReaxFF - reactive force field developed by Adri van Duin, William Goddard and coworkers. It is fast, transferable and is the computational method of choice for atomistic-scale dynamical simulations of chemical reactions.
- EVB (empirical valence bond) – This reactive force field, introduced by Warshel and coworkers, is probably the most reliable and physically consistent way of using force fields in modeling chemical reactions in different environments. The EVB facilitates calculations of actual activation free energies in condensed phases and in enzymes.
- RWFF - reactive force field for water developed by Detlef W. M. Hofmann, Liudmila N. Kuleshova and Bruno D'Aguanno. It is very fast, reproduces the experimental data of neutron scattering accurate, and allows to simulate the bond formation/breaking of water and acids.

[49]

Coarse-grained Force fields

- VAMM- Virtual atom molecular mechanics (VAMM) force field developed by Korkut and Hendrickson. VAMM is a coarse-grained force field specifically designed for molecular mechanics calculations such as large scale conformational transitions based on the virtual interactions of Calpha atoms. It is a knowledge based force field and formulated to capture features dependent on secondary structure and on residue-specific contact information in proteins [50]

Other

- VALBOND - a function for angle bending that is based on valence bond theory and works for large angular distortions, hypervalent molecules, and transition metal complexes. It can be incorporated into other force fields such as CHARMM and UFF.

Water Models

The set of parameters used to model water or aqueous solutions (basically a force field for water) is called a water model. Water has attracted a great deal of attention due to its unusual properties and its importance as a solvent. Many water models have been proposed; some examples are TIP3P, TIP4P, SPC, Flexible SPC, and ST2.

See also

- Force field implementation
- Molecular dynamics
- Molecular modelling
- Software for molecular mechanics modeling
- Statistical potential

Further reading

1. Schlick T. (2000). *Molecular Modeling and Simulation: An Interdisciplinary Guide* Interdisciplinary Applied Mathematics: Mathematical Biology. Springer-Verlag New York, NY.
2. Israelachvili, J.N. (1992) *Intermolecular and surface forces.* Academic Press, San Diego.
3. Warshel A (1991). "Computer Modeling of Chemical Reactions in Enzymes and Solutions" John Wiley & Sons New York.

References

[1] Ponder JW and Case DA. (2003) Force fields for protein simulations. *Adv. Prot. Chem.* 66: 27-85.

[2] Warshel A, Sharma PK, Kato M and Parson WW (2006) Modeling Electrostatic Effects in Proteins. Biochim. Biophys. Acta 1764:1647-1676.

[3] Schutz CN. and Warshel A. 2001. What are the dielectric "constants" of proteins and how to validate electrostatic models? Proteins 44: 400-417.

[4] Israelachvili, J.N. 1992. *Intermolecular and surface forces.* Academic Press, San Diego.

[5] Leckband, D. and Israelachvili, J. (2001) Intermolecular forces in biology. *Quart. Rev. Biophys.* 34: 105-267.

[6] Koehl P. and Levitt M. (1999) A brighter future for protein structure prediction. *Nature Struct. Biol.* 6: 108-111.

[7] Brunger AT and Adams PD. (2002) Molecular dynamics applied to X-ray structure refinement. *Acc. Chem. Res.* 35: 404-412.

[8] Guntert P. (1998) Structure calculation of biological macromolecules from NMR data. *Quart. Rev. Biophys.* 31: 145-237.

[9] Tramontano A. and Morea V. 2003. Assessment of homology-based predictions in CASP5. *Proteins.* 53: 352-368.

[10] Gohlke H. and Klebe G. (2002) Approaches to the description and prediction of the binding affinity of small-molecule ligands to macromolecular receptors. *Angew. Chem. Internat. Ed.* 41: 2644-2676.

[11] Edgcomb SP. and Murphy KP. (2000) Structural energetics of protein folding and binding. *Current Op. Biotechnol.* 11: 62-66.

[12] Lazaridis T. and Karplus (2000) Effective energy functions for protein structure prediction. *Curr. Op. Struct. Biol.* 10: 139-145

[13] Levitt M. and Warshel A. (1975) Computer Simulations of Protein Folding, Nature 253: 694-698

[14] Gordon DB, Marshall SA, and Mayo SL (1999) Energy functions for protein design. *Curr. Op. Struct. Biol.* 9: 509-513.

[15] Mendes J., Guerois R, and Serrano L (2002) Energy estimation in protein design. *Curr. Op. Struct. Biol.* 12: 441-446.

[16] Rohl CA, Strauss CEM, Misura KMS, and Baker D. (2004) Protein structure prediction using Rosetta. *Meth. Enz.* 383: 66-93.

[17] Lomize AL, Pogozheva ID, Lomize MA, Mosberg HI (2006) Positioning of proteins in membranes: A computational approach. *Protein Sci.* 15, 1318-1333.

[18] Lomize A.L., Reibarkh M.Y. and Pogozheva I.D. (2002) Interatomic potentials and solvation parameters from protein engineering data for buried residues. *Protein Sci.*, 11:1984-2000.

[19] Murphy K.P. and Gill S.J. 1991. Solid model compounds and the thermodynamics of protein unfolding. *J. Mol. Biol.*, 222: 699-709.

[20] Shakhnovich, E.I. and Finkelstein, A.V. (1989) Theory of cooperative transitions in protein molecules. I. Why denaturation of globular proteins is a first-order phase transition. *Biopolymers* 28: 1667-1680.

[21] Graziano, G., Catanzano, F., Del Vecchio, P., Giancola, C., and Barone, G. (1996) Thermodynamic stability of globular proteins: a reliable model from small molecule studies. *Gazetta Chim. Italiana* 126: 559-567.

[22] Myers J.K. and Pace C.N. (1996) Hydrogen bonding stabilizes globular proteins, *Biophys. J.* 71: 2033-2039.

[23] Scholtz J.M., Marqusee S., Baldwin R.L., York E.J., Stewart J.M., Santoro M., and Bolen D.W. (1991) Calorimetric determination of the enthalpy change for the alpha-helix to coil transition of an alanine peptide in water. *Proc. Natl. Acad. Sci. USA* 88: 2854-2858.

[24] Gavezotti A. and Filippini G. (1994) Geometry of intermolecular X-H...Y (X,Y=N,O) hydrogen bond and the calibration of empirical hydrogen-bond potentials. *J. Phys. Chem.* 98: 4831-4837.

[25] Norman L. Allinger. Conformational analysis. 130. MM2. A hydrocarbon force field utilizing V1 and V2 torsional terms. *J. Am. Chem. Soc.* **1977**, *99*, 8127-8134.

[26] MM2 and MM3's home page (http://europa.chem.uga.edu/allinger/mm2mm3.html)

[27] Allinger, N. L., Yuh, Y. H., & Lii, J-H. (1989) Molecular Mechanics. The MM3 Force Field for Hydrocarbons. 1. J. Am. Chem. Soc. 111, 8551-8565.

[28] Lii, J-H., & Allinger, N. L. (1989a) Molecular Mechanics. The MM3 Force Field for Hydrocarbons. 2. Vibrational Frequencies and Thermodynamics, J. Am. Chem. Soc. 111, 8566-8575.

[29] Lii, J-H., & Allinger, N. L. (1989b) Molecular Mechanics. The MM3 Force Field for Hydrocarbons. 3. The van der Waals Potentials and Crystal data for Aliphatic and Aromatic Hydrocarbons, J. Am. Chem. Soc. 111, 8576-8582.

[30] Schaumann, T., Braun, W. and Wutrich, K. (1990) The program FANTOM for energy refinement of polypeptides and proteins using a Newton-Raphson minimizer in torsion angle space. *Biopolymers* 29: 679-694.

[31] Margit Möllhoff, Ulrich Sternberg (2001) Molecular Mechanics with fluctuating atomic charges - a new force field with semi-empirical charge calculation *J. Mol. Model.* 7: 90-102

[32] http://www.igc.ethz.ch/gromos/

[33] http://zarbi.chem.yale.edu/

[34] http://laetro.usc.edu/programs/#molaris

[35] http://futura.usc.edu/programs/index.html#molaris

[36] http://msdlocal.ebi.ac.uk/docs/mmrefs.html#ecepp

[37] Warshel A (1973). Quantum Mechanical Consistent Force Field (QCFF/PI) Method: Calculations of Energies, Conformations and Vibronic Interactions of Ground and Excited States of Conjugated Molecules, Israel J. Chem. 11: 709.

[38] Warshel A and Levitt M (1974). QCFF/PI: A Program for the Consistent Force Field Evaluation of Equilibrium Geometries and Vibrational Frequencies of Molecules, QCPE 247, Quantum Chemistry Program Exchange, Indiana University.

[39] http://www.exorga.com/

[40] Warshel A. and Levitt M. (1976) Theoretical Studies of Enzymatic Reactions: Dielectric Electrostatic and Steric Stabilization of the Carbonium Ion in the Reaction of Lysozyme, J. Mol. Biol. 103: 227-249

[41] http://iqc.udg.es/~marcel/manuals/drf90/

[42] http://www.lct.jussieu.fr/pagesperso/jpp/

[43] N. Gresh, G. A. Cisneros, T. A. Darden and J-P Piquemal(2007) Anisotropic, polarizable molecular mechanics studies of inter-, intra-molecular interactions, and ligand-macromolecule complexes. A bottom-up strategy, J. Chem. Theory. Comput. 3: 1960

[44] http://dasher.wustl.edu/tinker/

[45] http://www-stone.ch.cam.ac.uk/programs.html

[46] J.-P. Piquemal, G. A. Cisneros, P. Reinhardt, N. Gresh and T. A. Darden (2006), Towards a a Force Field based on Density Fitting., J. Chem. Phys. 124: 104101

[47] G. A. Cisneros, J-P. Piquemal and T. A. Darden (2006), Generalization of the Gaussian Electrostatic Model: extension to arbitrary angular momentum, distributed multipoles and speedup with reciprocal space methods, J. Chem. Phys. 125:184101

[48] Ulrich Sternberg, Frank-Thomas Koch and Margit Möllhoff (1994) New Approach to the Semiempirical Calculation of Atomic Charges for Polypeptides and Large Molecular Systems *J. Comp. Chem.* 15: 524-531

[49] D.W.M. Hofmann, L. N. Kuleshova, B. D'Aguanno (2007) A new reactive potential for the Molecular Dynamics simulation of liquid water. Chem.Phys.Lett. 448: 138-143

[50] Korkut A, Hendrickson WA (2009) A force field for virtual atom molecular mechanics of proteins. Proc Natl Acad Sci USA 106:15667−15672

CHARMM

Developer(s)	Martin Karplus, Accelrys
Initial release	1983
Stable release	c35b3 / August 15, 2009
Preview release	c36a3 / August 15, 2009
Written in	FORTRAN 77/95
Operating system	Unix-like
Type	molecular dynamics
License	The CHARMM Development Project
Website	charmm.org [1]

CHARMM (**Chemistry at HARvard Macromolecular Mechanics**) is the name of a widely used set of force fields for molecular dynamics as well as the name for the molecular dynamics simulation and analysis package associated with them.[2] [3] The CHARMM Development Project involves a network of developers throughout the world working with Martin Karplus and his group at Harvard to develop and maintain the CHARMM program. Licenses for this software are available, for a fee, to people and groups working in academia.

The commercial version of CHARMM, called **CHARMm** (note the lowercase 'm'), is available from Accelrys.

CHARMM force fields

The CHARMM force fields for proteins include: united-atom (sometimes called "extended atom") CHARMM19[4], all-atom CHARMM22[5] and its dihedral potential corrected variant CHARMM22/CMAP.[6] In the CHARMM22 protein force field, the atomic partial charges were derived from quantum chemical calculations of the interactions between model compounds and water. Furthermore, CHARMM22 is parametrized for the TIP3P explicit water model. Nevertheless, it is frequently used with implicit solvents. In 2006, a special version of CHARMM22/CMAP was reparametrized for consistent use with implicit solvent GBSW.[7]

For DNA, RNA, and lipids, CHARMM27[8] is used. Some force fields may be combined, for example CHARMM22 and CHARMM27 for the simulation of protein-DNA binding. Additionally, parameters for NAD+, sugars, fluorinated compounds, etc. may be downloaded. These force field version numbers refer to the CHARMM version where they first appeared, but may of course be used with subsequent versions of the CHARMM executable program. Likewise, these force fields may be used within other molecular dynamics programs that support them.

In 2009, a general force field for drug-like molecules (CGenFF) was introduced. It "covers a wide range of chemical groups present in biomolecules and drug-like molecules, including a large number of heterocyclic scaffolds." [9] The general force field is designed to cover any combination of chemical groups. This inevitably comes with a decrease in accuracy for representing any particular subclass of molecules. Users are repeatedly warned in Mackerell's website not to use the CGenFF parameters for molecules for which specialized force fields already exist (as mentioned above for proteins, nucleic acids, etc).

CHARMM also includes polarizable force fields using two approaches. One is based on the fluctuating charge (FQ) model, also known as Charge Equilibration (CHEQ). [10] [11] The other is based on the Drude shell or dispersion oscillator model. [12] [13]

Parameters for all of these force fields may be downloaded from the Mackerell website [14] for free.

CHARMM molecular dynamics program

The CHARMM program allows generation and analysis of a wide range of molecular simulations. The most basic kinds of simulation are minimization of a given structure and production runs of a molecular dynamics trajectory.

More advanced features include free energy perturbation (FEP), quasi-harmonic entropy estimation, correlation analysis and combined quantum, and molecular mechanics (QM/MM) methods.

CHARMM is one of the oldest programs for molecular dynamics. It has accumulated a huge number of features, some of which are duplicated under several keywords with slight variations. This is an inevitable result of the large number of outlooks and groups working on CHARMM throughout the world. The changelog file [15] as well as CHARMM's source code are good places to look for the names and affiliations of the main developers. The involvement and coordination by Charles L. Brooks III's group at the University of Michigan is very salient.

History of the program

Around 1969, there was considerable interest in developing potential energy functions for small molecules. CHARMM originated at Martin Karplus's group at Harvard. Karplus and his then graduate student Bruce Gelin decided the time was ripe to develop a program that would make it possible to take a given amino acid sequence and a set of coordinates (e.g., from the X-ray structure) and to use this information to calculate the energy of the system as a function of the atomic positions. Karplus has acknowledged the importance of major inputs in the development of the (at the time nameless) program, including

- Schneior Lifson's group at the Weizmann Institute, especially from Arieh Warshel who went to Harvard and brought his consistent force field (**CCF**) program with him;
- Harold Scheraga's group at Cornell University; and
- Awareness of Michael Levitt's pioneering energy calculations for proteins

In the 1980s, finally a paper appeared and CHARMM made its public début. Gelin's program had by then been considerably restructured. For the publication, Bob Bruccoleri came up with the name HARMM (HARvard Macromolecular Mechanics), but it didn't seem appropriate. So they added a C for Chemistry. Karplus said: "I sometimes wonder if Bruccoleri's original suggestion would have served as a useful warning to inexperienced scientists working with the program."[16] CHARMM has continued to grow and the latest release of the executable program was made in August 2008 as CHARMM35b1.

Running CHARMM Under Unix/Linux

The general syntax for using the program is:

```
charmm -i filename.inp -o filename.out
```

charmm

   The actual name of the program (or script which runs the program) on the computer system being used.

filename.inp

   A text file which contains the CHARMM commands. It starts by loading the molecular topologies (top) and force field (par). Then one loads the molecular structures' Cartesian coordinates (e.g. from PDB files). One can then modify the molecules (adding hydrogens, changing secondary structure). The calculation section can include energy minimization, dynamics production, and analysis tools such as motion and energy correlations.

filename.out

   The log file for the CHARMM run, containing echoed commands, and various amounts of command output. The output print level may be increased or decreased in general, and procedures such as minimization and dynamics have printout frequency specifications. The values for temperature, energy pressure, etc. are output

at that frequency.

CHARMM and Volunteer Computing

Docking@Home, hosted by University of Delaware, one of the projects which use a opensource platform for the distributed computing, BOINC, adopts CHARMM to analyze the atomic details of protein-ligand interactions in terms of Molecular Dynamics (MD) simulations and minimizations.

World Community Grid, sponsored by IBM, runs a project called The Clean Energy Project [17] which also uses CHARMM.

See also

- AMBER
- Ascalaph Designer
- GROMACS
- Force field implementation
- List of software for molecular mechanics modeling
- MDynaMix
- OPLS
- Yasara

External links

- Accelrys website [18]
- CHARMM website [1] with documentation [19] and helpful discussion forums [20]
- CHARMM tutorial [21]
- MacKerell [22] website including a Package of force field parameters for CHARMM [14]
- C.Brooks website [23]
- CHARMM page at Harvard [24]
- Roux website [25]
- Bernard R. Brooks Group Website [26]
- VMD [27] - visualization of CHARMM trajectories
- Sirius [28] - visualization of CHARMM trajectories
- Docking@Home [29]
- CHARMM-GUI project [30]

References

[1] http://www.charmm.org/

[2] Brooks BR, Bruccoleri RE, Olafson BD, States DJ, Swaminathan S, Karplus M (1983). "CHARMM: A program for macromolecular energy, minimization, and dynamics calculations". *J Comp Chem* **4**: 187–217. doi: 10.1002/jcc.540040211 (http://dx.doi.org/10.1002/jcc.540040211).

[3] MacKerell, A.D., Jr.; Brooks, B.; Brooks, C. L., III; Nilsson, L.; Roux, B.; Won, Y.; Karplus, M. (1998). "CHARMM: The Energy Function and Its Parameterization with an Overview of the Program". in Schleyer, P.v.R.; et al.. *The Encyclopedia of Computational Chemistry*. **1**. Chichester: John Wiley & Sons. pp. 271–277.

[4] Reiher, III WH (1985). "Theoretical studies of hydrogen bonding". *PhD Thesis at Harvard University*.

[5] MacKerell, Jr. AD, *et al.* (1998). "All-atom empirical potential for molecular modeling and dynamics studies of proteins". *J Phys Chem B* **102**: 3586–3616. doi: 10.1021/jp973084f (http://dx.doi.org/10.1021/jp973084f).

[6] MacKerell, Jr. AD, Feig M, Brooks, III CL (2004). "Extending the treatment of backbone energetics in protein force fields: limitations of gas-phase quantum mechanics in reproducing protein conformational distributions in molecular dynamics simulations". *J Comput Chem* **25**: 1400–1415. doi: 10.1002/jcc.20065 (http://dx.doi.org/10.1002/jcc.20065).

[7] Brooks CL, Chen J, Im W (2006). "Balancing solvation and intramolecular interactions: toward a consistent generalized born force field (CMAP opt. for GBSW)". *J Am Chem Soc* **128**: 3728–3736. doi: 10.1021/ja057216r (http://dx.doi.org/10.1021/ja057216r).

[8] MacKerell, Jr. AD, Banavali N, Foloppe N (2001). "Development and current status of the CHARMM force field for nucleic acids". *Biopolymers* **56**: 257–265. doi: 10.1002/1097-0282(2000)56:4<257::AID-BIP10029>3.0.CO;2-W (http://dx.doi.org/10.1002/1097-0282(2000)56:4<257::AID-BIP10029>3.0.CO;2-W).

[9] K. Vanommeslaeghe, E. Hatcher, C. Acharya, S. Kundu, S. Zhong, J. Shim, E. Darian, O. Guvench, P. Lopes, I. Vorobyov, A. D. Mackerell Jr. * (2009). "CHARMM general force field: A force field for drug-like molecules compatible with the CHARMM all-atom additive biological force fields". *J Comput Chem*. doi: 10.1002/jcc.21367 (http://dx.doi.org/10.1002/jcc.21367).

[10] Patel, S.; MacKerell, Jr. AD; Brooks III, Charles L (2004). "CHARMM fluctuating charge force field for proteins: I parameterization and application to bulk organic liquid simulations". *J Comput Chem* **25**: 1–15. doi: 10.1002/jcc.10355 (http://dx.doi.org/10.1002/jcc.10355).

[11] Patel, S.; MacKerell, Jr. AD; Brooks III, Charles L (2004). "CHARMM fluctuating charge force field for proteins: II protein/solvent properties from molecular dynamics simulations using a nonadditive electrostatic model". *J Comput Chem* **25**: 1504–1514. doi: 10.1002/jcc.20077 (http://dx.doi.org/10.1002/jcc.20077).

[12] Lamoureux G, Roux B. (2003). Modeling induced polarization with classical Drude oscillators: Theory and molecular dynamics simulation algorithm. *J Chem Phys* 119(6):3025-3039.

[13] Lamoureux G, Harder E, Vorobyov IV, Roux B, MacKerell AD. (2006). A polarizable model of water for molecular dynamics simulations of biomolecules. *Chem Phys Lett* 418:245-9.

[14] http://mackerell.umaryland.edu/CHARMM_ff_params.html

[15] http://www.charmm.org/package/changelogs/c34log.shtml

[16] Karplus M (2006). "Spinach on the ceiling: a theoretical chemist's return to biology". *Annu Rev Biophys Biomol Struct* **35**: 1–47. doi: 10.1146/annurev.biophys.33.110502.133350 (http://dx.doi.org/10.1146/annurev.biophys.33.110502.133350).

[17] http://www.worldcommunitygrid.org/projects_showcase/cep1/viewCep1Main.do

[18] http://www.accelrys.com/

[19] http://www.charmm.org/html/documentation/chmdoc.html

[20] http://165.112.184.13//ubbthreads/ubbthreads.php?Cat=

[21] http://www.ch.embnet.org/MD_tutorial/

[22] http://www.pharmacy.umaryland.edu/faculty/amackere/

[23] http://www.scripps.edu/brooks/

[24] http://yuri.harvard.edu/

[25] http://thallium.bsd.uchicago.edu/RouxLab/index.html

[26] http://www.lobos.nih.gov/cbs/index.php

[27] http://www.ks.uiuc.edu/Research/vmd/

[28] http://sirius.sdsc.edu

[29] http://docking.cis.udel.edu/

[30] http://www.charmm-gui.org/

MDynaMix

MDynaMix [1] [2] (an acronym for *Molecular Dynamics of Mixtures*) is a general purpose molecular dynamics software package for simulations mixtures of molecules, interacting by AMBER/CHARMM like force fields in a periodic boundary conditions. MDynaMix is developed at the Stockholm University, Sweden. Algorithms for NVE, NVT, NPT and anisotropic NPT ensembles are employed, as well as Ewald summation for treatment of the electrostatic interactions. The code was written in Fortran 77 (with MPI for parallel execution) and C++ and released under the GNU GPL. Package works on Unix/Linux workstations and clusters of workstations as well as on Windows in sequential mode.

DNA simulation on MDynaMix
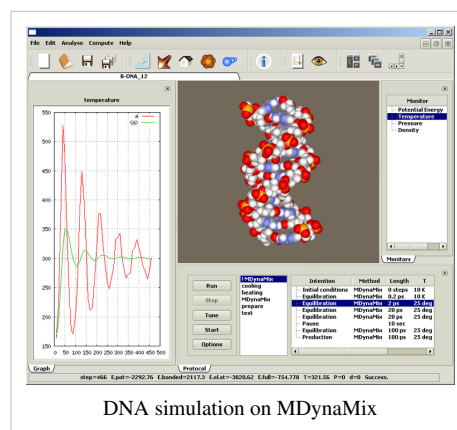
Programs

- **md** - the main MDynaMix block
- **makemol** is an utility which provides help in creation of files describing molecular structure and the force field
- **tranal** is a suite of utilities for analyzing trajectories
- **mdee** is a version of the program which implement expanded ensemble method for computation of free energy / chemical potential (is not parallelized)
- **mge** provides graphical interface for molecular models construction and monitoring of dynamics process

Field of application

- Thermodynamic properties of liquids [3]
- Nucleic acid - ions interaction [4]
- Modeling of lipid bilayers[5]
- Polyelectrolytes[6]
- Ionic liquids[7] [8]
- X-ray spectra of liquid water[9]
- Force Field development[10] [11]

See also

- Abalone
- BOSS
- CHARMM
- GROMACS
- Molecular modelling
- Molecular design software
- NAMD
- TINKER

External links

- Home page [12]
- Graphical shell for MDynaMix [30]

References

[1] A.P.Lyubartsev, A.Laaksonen (2000). "MDynaMix - A scalable portable parallel MD simulation package for arbitrary molecular mixtures". *Computer Physics Communications* **128**: 565−589.

[2] A.P.Lyubartsev, A.Laaksonen (1998). "Parallel molecular dynamics simulations of biomolecular systems". *Applied Parallel Computing Large Scale Scientific and Industrial Problems*. Lecture Notes in Computer Science. **1541**. Heidelberg: Springer Berlin. pp. 296−303. doi: 10.1007/BFb0095310 (http://dx.doi.org/10.1007/BFb0095310). ISBN 978-3-540-65414-8.

[3] T. Kuznetsova and B. Kvamme (2002). "Thermodynamic properties and interfacial tension of a model water−carbon dioxide system". *Phys. Chem. Chem. Phys.* **4**: 937−941.

[4] Y. Cheng, N. Korolev and L. Nordenskiöld (2006). "Similarities and differences in interaction of K^+ and Na^+ with condensed ordered DNA. A molecular dynamics computer simulation study". *Nucleic Acids Research* **34**: 686−696.

[5] C.-J. Högberg, A.M.Nikitin and A.P. Lyubartsev (2008). "Modification of the CHARMM force field for DMPC lipid bilayer". *Journal of Computational Chemistry* **29**: 2359−2369.

[6] A. Vishnyakov and A.V. Neimark (2008). "Specifics of solvation of sulfonated polyelectrolytes in water, dimethylmethylphosphonate, and their mixture: A molecular simulation study". *J. Chem. Phys.* **128**: 164902.

[7] G. Raabe and J. Köhler (2008). "Thermodynamical and structural properties of imidazolium based ionic liquids from molecular simulation". *J. Chem. Phys.* **128**: 154509.

[8] X. Wu, Z. Liu, S. Huang and W. Wang (2005). "Molecular dynamics simulation of room-temperature ionic liquid mixture of [bmim][BF_4] and acetonitrile by a refined force field". *Phys. Chem. Chem. Phys.* **7**: 2771−2779.

[9] R.L.C. Wang, H.J. Kreuzer and M. Grunze (2006). "Theoretical modeling and interpretation of X-ray absorption spectra of liquid water". *Phys. Chem. Chem. Phys.* **8**: 4744−4751.

[10] A.M. Nikitin and A.P. Lyubartsev (2007). "A new six-site acetonitrile model for simulations of liquid acetonitril and its aqueous mixture". *J. Comp. Chem.* **28**: 2020−2026.

[11] E.S. Böesa, E. Bernardia, H. Stassena, P.F.B. Gonçalves (2008). "Solvation of monovalent anions in formamide and methanol: Parameterization of the IEF-PCM model". *Chemical Physics* **344**: 101−113.

[12] http://people.su.se/~lyuba/mdynamix/

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